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Diseases *of the* Nervous System

A Practical Journal on Psychiatry and Neurology

(CONTENTS ON PAGE 654)

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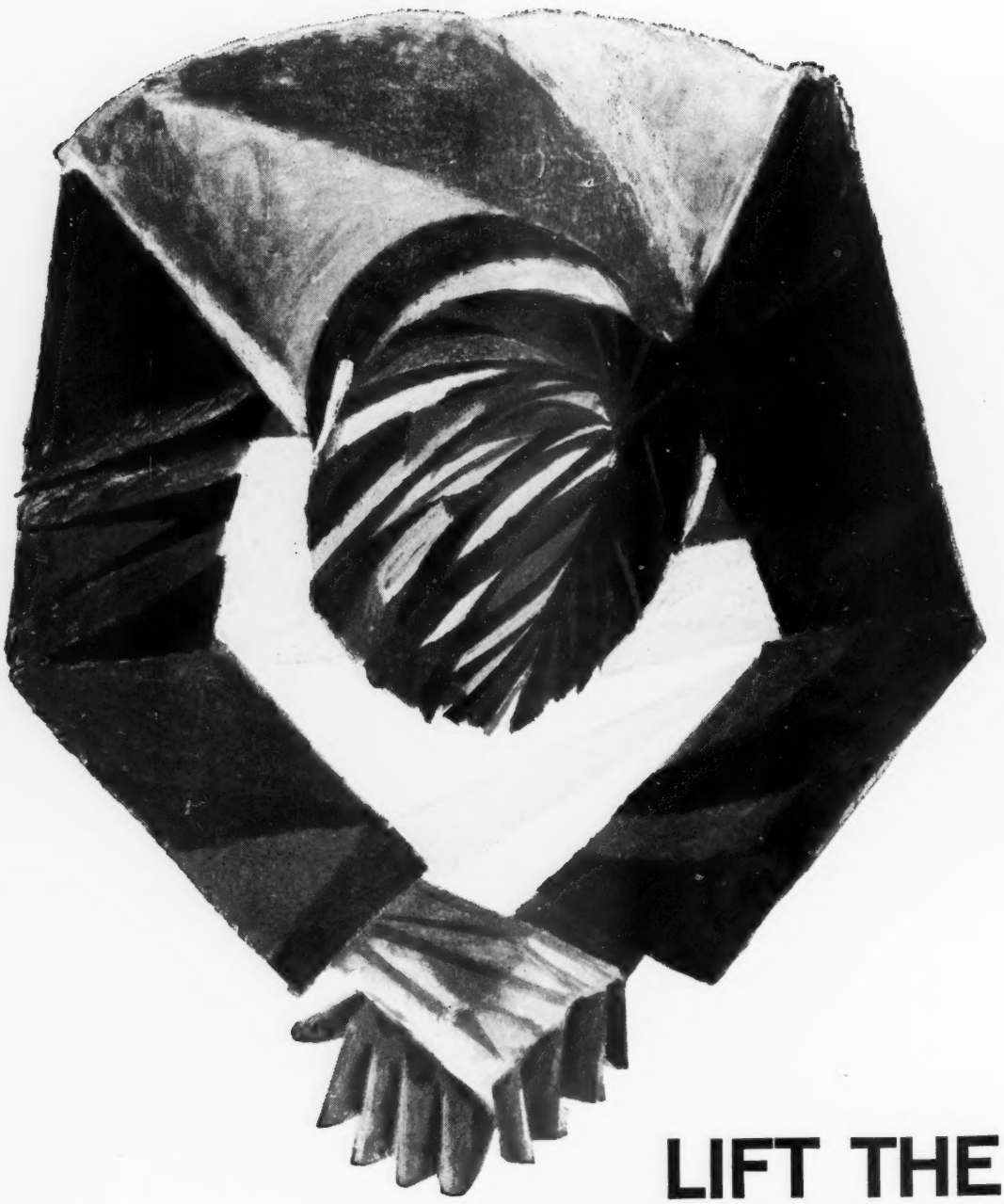

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Volume XXII DECEMBER 1961 Number 12

DISEASES *of the* Nervous System

Contents

CONCEPT OF HOMEOSTASIS IN THE CENTRAL NERVOUS SYSTEM 667
George Paulson

RECENT DEVELOPMENTS IN PSYCHOANALYTIC RESEARCH 671
Robert B. White

PSYCHOSOMATIC ASPECTS OF HYPERADRENOCORTICISM TREATED WITH CHLORPROMAZINE 680
Noble A. Endicott and Alexander Grainick

THE PLACE OF INSULIN IN PSYCHIATRIC TREATMENT 687
Edwin Dunlop

EFFECT OF DRUGS ON "POOR" TREATMENT CASES 692
Antioco R. Barron, Lester H. Rudy and Jackson A. Smith

FRENQUEL CORRECTS EEG CHANGES AND RELIEVES SYMPTOMS IN PORPHYRIA 695
Z. S. Sikes

THE STATUS AND USEFULNESS OF THE PSYCHIATRIST 697
Thomas R. Kearney

CLINICAL NEUROPATHOLOGICAL CONFERENCE 700
Stanley M. Aronson and Haruo Okazaki

INDEX 705

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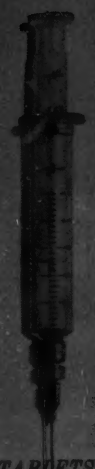

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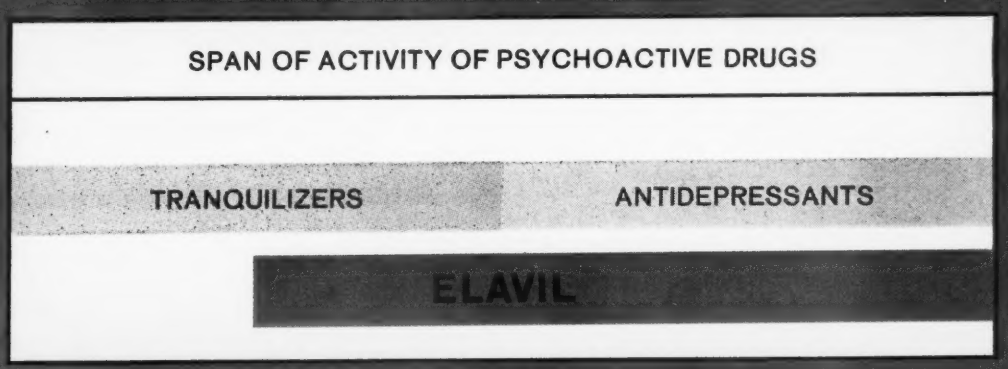

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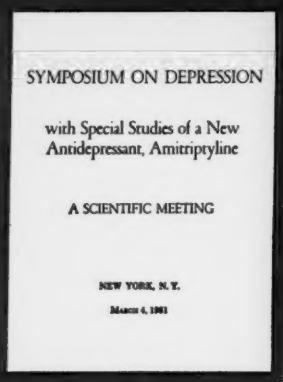

SYMPOSIUM ON DEPRESSION
with Special Studies of a New Antidepressant, Amitriptyline
A SCIENTIFIC MEETING
NEW YORK, N.Y.
March 4, 1961

EXCERPTS FROM A SYMPOSIUM ON DEPRESSION

ELAVIL

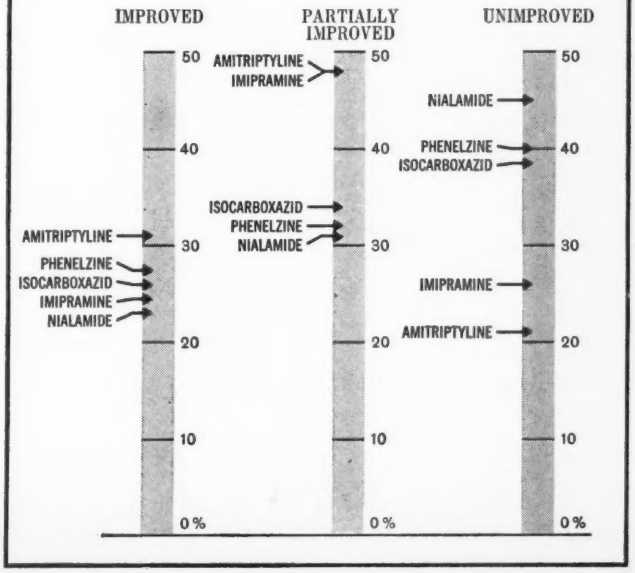
AMITRIPTYLINE HYDROCHLORIDE

INVESTIGATOR	FINDINGS
DUNLOP, EDWIN: The treatment of depression in private practice.	"Amitriptyline [ELAVIL] has a specific advantage over any antidepressant currently available and I see increasing evidence of its usefulness in reducing tension, agitation and anxiety, as well as in relieving the depressive quality of the illness. Amitriptyline appears . . . to combine better than any other antidepressant drug the successful treatment of anxiety at one end of the scale and depression at the other. Experience in the past has shown us that, when using electroshock or analeptics, although depression can be relieved, the accompanying anxiety eventually proves more troublesome than the depressive phase of the illness. Amitriptyline successfully bridges these divergent symptoms which are displayed in varying proportions in all depressive syndromes. ". . . Approximately one hundred and twenty patients have been studied with amitriptyline during the last fifteen months. It is an effective antidepressant when employed in both hospital and ambulatory patients. Its dependability and freedom from toxicity and severe side effects merit further evaluation on a broader spectrum of depressive disorders."
BENNETT, DOUGLAS: Treatment of depressive states with amitriptyline.	"In those cases showing a good response, early and dramatic improvement in sleeplessness resulted and many patients noted a feeling of relaxation. The ability of some patients to reduce their night sedatives after only a month's treatment was unique in my experience of the treatment of depression."
SAUNDERS, JOHN C.: Antidepressives: the pith of affective therapy.	"Its primary action in hospitalized psychotics is antidepressive; this along with its very low rate of side actions make it a drug of potentially frequent application in a broad spectrum of neuropsychiatric diseases. . . . Since a large part of any hospital population will reach a plateau if given only a tranquilizer or an energizer, we suggest that amitriptyline alone be given prior to combination therapy, as this drug is easier and safer to administer and produces a significant improvement in a high percentage of cases (60-75)."
OSTFELD, ADRIAN M.: Effects of an antidepressant drug on tests of mood and perception.	"Finally, it appears that amitriptyline in the doses employed here is relatively effective in depressed states of neurotic proportions. Its freedom from severe side effects in doses that are therapeutically effective seems established in this patient population."

(This symposium was published in
Diseases of the Nervous System,
Volume 22, Section Two—Supplement, May 1961)

INVESTIGATOR	FINDINGS
AYD, FRANK J., JR.: A critique of antidepressants.	"Amitriptyline and imipramine induce similar side effects but, generally speaking, those of amitriptyline cause less subjective discomfort in patients than those of imipramine. "... Many of the factors that favor a satisfactory response to these drugs are also those clinically associated with the expectation of a good reaction to ECT. The danger lies in their general slowness in taking effect which makes their use hazardous for severely depressed suicidal patients who, preferably, should be treated with electroshock therapy. Otherwise, these compounds can be a satisfactory substitute for shock therapy for most depressed patients. Thus, these drugs have lessened the need for ECT. On those occasions when ECT is necessary, if the shock therapy is combined with an antidepressant, ECT can be dispensed with after a few treatments."

COMPARISON OF THERAPEUTIC RESULTS WITH VARIOUS ANTIDEPRESSANTS



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EXCERPTS FROM A SYMPOSIUM ON DEPRESSION (continued)

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INVESTIGATOR	FINDINGS
DORFMAN, WILFRED: Masked depression.	"In evaluating the effectiveness of amitriptyline in all these different settings, it was considered to be effective in 17 of the 25 patients (68%)."
FELDMAN, PAUL E.: Psychotherapy and chemotherapy (amitriptyline) of anergic states.	"Compared to other energizer compounds, particularly the hydrazines, amitriptyline appears to be relatively nontoxic. The laboratory reports for the most part remained within normal limits. Occasionally, abnormal readings were reported, but these appeared only sporadically and were not related to any clinical findings."

INDICATIONS: manic-depressive reaction—depressed phase; involutional melancholia; reactive depression; schizoaffective depression; neurotic-depressive reaction; and these target symptoms: anxiety; depressed mood; insomnia; psychomotor retardation; functional somatic complaints; loss of interest; feelings of guilt; anorexia. May be used whether the emotional difficulty is a manifestation of neurosis or psychosis,[1] and in ambulatory or hospitalized patients.[1,2,3]

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The natural course of depression is often many months in duration. Accordingly, it is appropriate to continue maintenance therapy for at least three months after the patient has achieved satisfactory improvement in order to lessen the possibility of relapse, which may occur if the patient's depressive cycle is not complete. In the event of relapse, therapy with ELAVIL may be reinstituted.

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bibliography

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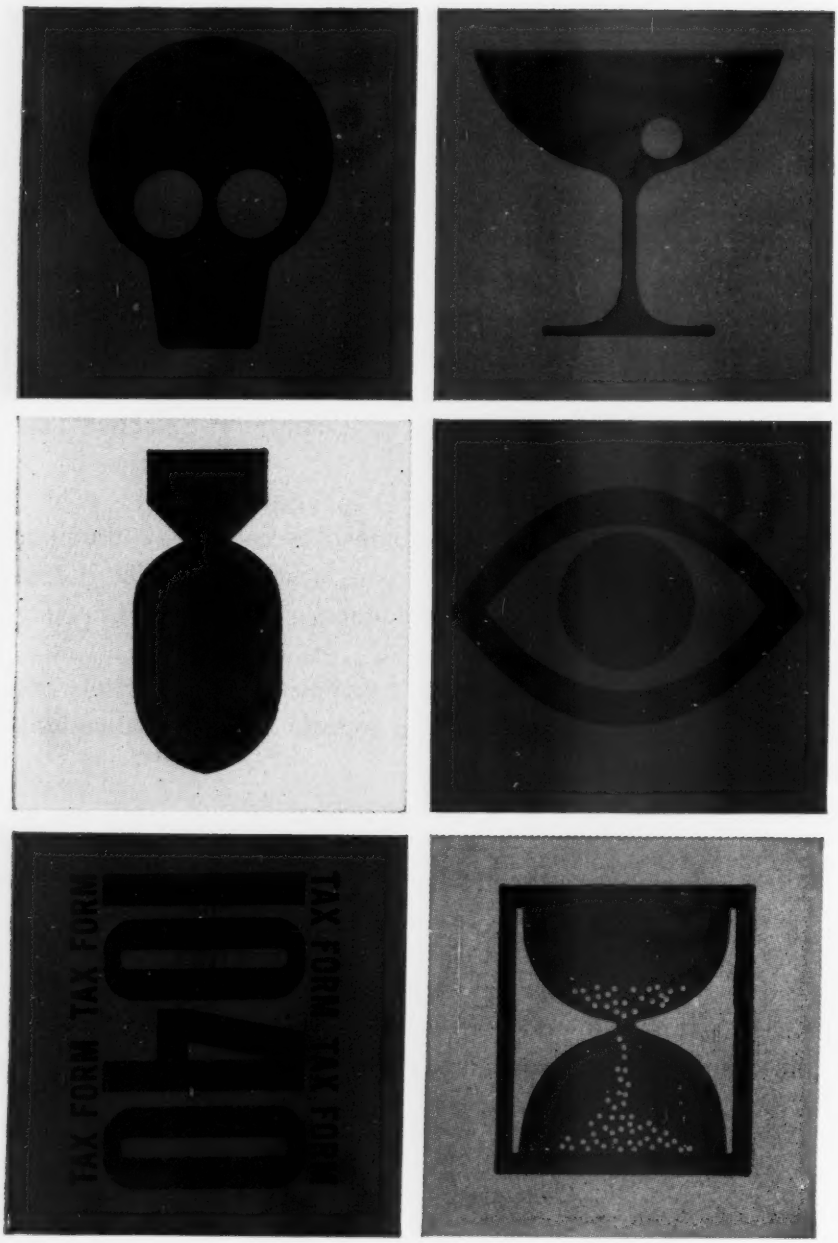

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References.

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DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Concept of Homeostasis in the Central Nervous System

GEORGE PAULSON, CAPT. M.C.

There is increased interest in relating facts from neurophysiology and neurochemistry to clinical observations from neurology and psychiatry. Through the years a few general interpretations of physiologic functions have appeared repeatedly and are being reused as the new facts accumulate. This paper attempts to demonstrate the importance of one general physiologic concept, homeostasis, in explanations of neurologic and psychiatric conditions. The possible benefit of such effort is renewed emphasis on a general somatic theory that has often aided in the accumulation of new facts.

Neurology

A disturbance in balance between elements of the CNS is frequently offered as an explanation of signs seen in neurologic disease. Too much, too little, or too rapid a change in activity seems to account for many common clinical observations. Parkinsonism, pseudobulbar palsy, and spinal cord transection have been chosen to illustrate homeostasis in widely separate areas of the nervous system.

(1) There are many symptoms in the *Parkinson syndrome* and the pathologic changes are varied and numerous. Patients with parkinsonism may have lesions in the reticular formation and the cerebral cortex, but destruction is particularly prominent in the globus pallidus, substantia nigra, and other nuclei of the basal ganglia. It is still not clear how damage to extrapyramidal areas produces the clinical symptoms. Most physiologic explanations of parkinsonism invoke the concept of a distortion in a normal relation between two or more areas of the CNS. For example, a current neurology text mentions interruption in a reverberating circuit which involves the cerebral cortex, basal ganglia, and thalamus.[1]

As a minimum, any successful theory of parkinsonism must account for tremor and rigidity. In 1914 Kinnier-Wilson suggested that hyperkinetic states such as tremor resulted from activity of the cerebral cortex when it was no longer adequately "steadied" by basal ganglia.[2] More recently it has been suggested that the central basis for tremor is the interneuronal bulbospinal system.[3] Thalamic and pallidal structures are thought to exert a facilitative effect on tremor which originates in lower structures. Among recent theories of parkinsonian rigidity are those which invoke the afferent gamma system. "In parkinsonian rigidity the quick adaptive mechanism of the gamma system is defective and the tonic alpha system is overactive."[3] This is reflected clinically by failure in the rapid adjustment of muscle length in the parkinsonian patient. The elements of muscle regulation which are still intact maintain a constant muscle tension when released from higher control.

The definitive explanation of parkinsonian rigidity and tremor is unknown. Even the complete reason for benefit following pallidal destructive procedures is obscure. Nevertheless, it is likely that future explanations of parkinsonism will still include the concept of too much or too little activity, and a resulting disequilibrium between units of the CNS.

(2) *Pseudobulbar palsy* is a well accepted clinical syndrome in which pathologic changes in both cerebral hemispheres seem to cause dysfunction of the medulla oblongata. Spastic muscles innervated by the medulla produce difficulty in swallowing and

From Womack Army Hospital, Fort Bragg, North Carolina.

talking and the patients may be emotionally labile. Recent work has demonstrated that patients with pseudobulbar palsy also have hypersensitivity of the respiratory centers.[4] These various changes seen in pseudobulbar palsy are commonly attributed to failure of cortical inhibition. Inadequate regulatory impulses proceed down from above, and the lower areas are therefore relatively uncontrolled and overactive.

(3) *Spinal cord transection* is a devastating and dramatic clinical experiment in which spinal shock and the return of reflex function are the two striking features. Spinal shock is usually attributed to sudden loss of facilitative impulses from higher centers in the nervous system. In a sense, spinal shock represents a raised spinal threshold of reflexes.

Various reasons are offered as explanations for the return of reflex function after spinal transection. Most frequently return of reflexes is attributed, as might be anticipated, to lowering of the threshold of reflexes as spinal shock disappears. Spinal centers are assumed to become more responsive, more active, with the passage of time. As pointed out by Denny-Brown "removal of one of the competing factors in the control of movement at any level results in overactivity of the others."[5]

Psychiatry

Neurologic syndromes are closely associated with known pathologic changes. Psychiatric classification is less securely based on pathologic or physiologic evidence; and signs and symptoms remain the basis for classification of the functional psychoses. Depression, hallucinations, and anxiety have been selected for discussion on the basis of their frequency as symptoms of psychiatric disorders. The discussion will be concerned solely with somatic explanations which have been offered for these symptoms.

(1) There have been several somatic etiologies proposed to explain *depressive states.* These theories of depression are predominantly neurophysiologic or neurochemical; both utilize the concept of a proper neurologic equilibrium.

The neurophysiologic theories suggest a primary diencephalic origin for depressive symptoms. As integrator site, regulator, or recipient of impulses, the diencephalon is frequently associated with affect and emotion. Extensive summaries of experimental data relating the diencephalon and emotion appear in recent neurophysiology texts. There is less known about the effects of peripheral regions on the subcortical areas involved in emotional states.

Among the theories of depression are several that attribute emotional changes to a shift in a presumed balance between subcortical, neocortical, and reticular areas. Either increased inhibition from the cortex, or decreased intrinsic activity of subcortical areas could produce attenuation of function in subcortical regions. It has also been postulated that decreased activity in the region of the reticular formation can produce "inadequate alerting" of the upstream areas involved in emotions.[6] Other speculation regarding increased or decreased activity in the neocortical-diencephalic-reticular axis can be found.[7] Most theories postulate a primary diencephalic disorder in depression, with other areas secondarily influencing functions of the diencephalon. Since the fundamental feature is an equilibrium between neocortex and diencephalon, or between reticular substance and diencephalon, identical clinical states could conceivably be produced by too much at one end or too little at the other. Furthermore there is varied activity in subgroups of cell populations and it has been postulated that there is interaction between facilitative and inhibitory portions of the diencephalon itself.[8]

There are few neurochemical theories of depression. In 1954 Sperry[9] emphasized the lack of good experimental data for a biochemical theory of depression; many of his comments still apply. Sperry felt that one possible cause of depression is excess formation of aldehydes by the oxidative deamination of amines. There has been interest more recently in abnormal levels of cerebral serotonin. Some of the newer anti-depressant drugs are considered to be effective pri-

marily through inhibition of monoamine oxidases.

(2) *Hallucinations.* In addition to hallucinations found in functional psychiatric disease, there are also hallucinations which result from definite organic sources. Hallucinations are found with toxic or anoxic states, encephalitis, neoplasms, and convulsive disorders. A current psychiatric text states that in such organic conditions "there is perhaps an irritation of the association centers connected with the special sense hallucinated."[10] Electric currents, presumably excitatory, can certainly induce hallucinations when applied to cortical areas. Such hallucinations range from flashing, indistinct lights with occipital lobe stimulation to "memory hallucinations" produced by temporal lobe stimulation.[11] These hallucinations, most simply, appear related to overactivity of local cortical areas.

The relation of sensory input and hallucinations is of persistent interest. The relation of sensory input and cortex attracted Hughlings Jackson when he discussed hallucinations. "I believe that they are often really illusions, arising from external conditions, from morbid states of peripheral parts, or of lower sensory centres. They result from irritations propagated up to the highest centres, that is, to the uncontrolled, and thus over-ready-to-act, nervous arrangements left in these centres."[12] Recent studies of the action of hallucinogens point to drug effects on peripheral sensory structures.[13]

It is difficult to find any general physiologic theory of hallucinations, though psychologic theories abound. Marrazzi[14] discusses synaptic inhibition as a mechanism of hallucinations, and offers some supporting data. He mentions "release from cortical restraint," and "differential inhibition of dendritic over somatic synapses." He suggests "the form of dissociation from reality known as hallucination may sometimes result from an actual dissociation of primary visual inflow from its association areas."

It can be seen that in the several theories of hallucination the general theme of overactivity or underactivity remains. In hallucinations the recurrent theme is one of imbalance at the two extremes of cortex and peripheral sensory input.

(3) The literature of *anxiety* is immense and references can be selected as support for almost any theory. A few general observations are relevant regarding the well-known somatic accompaniment of anxiety. Anxiety is reflected in several body regions including musculoskeletal, gastrointestinal, cardiovascular, and respiratory systems. Most of the physical changes are in the direction of overactivity in a setting of anxiety. The neurologic association of these somatic changes is indefinite, and these bodily areas are represented in several areas of the CNS, including particularly the brain stem.

It is known that amphetamine can produce many of the physical symptoms of anxiety. This drug affects several areas of the CNS, but particularly the brain stem.[15] The reticular formation of the brain stem has also been the focus of much recent experimental work on EEG arousal responses. With a behavioral shift from sleep to extreme alertness, there is some shift in the EEG toward the appearance of an EEG arousal response. The exact relation of EEG arousal and behavioral arousal is not clear-cut or definite at the present time. Though EEG arousal can be produced in numerous ways, one of the fundamental methods is stimulation of the reticular activating system of the brain stem.

The effect of anxiety on learning has been studied repeatedly. Moderate anxiety speeds learning but larger amounts of anxiety inhibit the learning process. Similarly Furster[16] points to an increase in rate of learning with slight stimulation of the reticular activating system. A possible mechanism for the effect of anxiety on learning is offered by Bremer who indicates that ascending reticular impulses can produce either facilitation of the excitability of cortical interneurons or can produce a supraliminal excitation which actually inhibits the specific sensory impulses.

As indicated, the literature on anxiety is large and tenuous threads can be pulled to-

gether to support any thesis. It does appear that much of the current interest in neurologic substrate for anxiety can be directed at brain stem areas. It seems probable that the activity of higher areas is also of importance in the production, or regulation of anxiety.

Vigor of Homeostasis

The concept of levels of function in the CNS has broadened to include not only primary functions of major regions of the nervous system, but also effects produced by relations between the major regions. Sometimes interdependence of areas can be demonstrated experimentally, and additional projects can be planned to explore reciprocal relations in different cell populations. With or without experimental data, however, the concept of a proper neurologic equilibrium is useful to explain clinical phenomena. Built into the concept of neurologic equilibrium or homeostasis is the basic theme of (1) too much, (2) too little, (3) or too rapidly changing (as emphasized by Hallowell Davis).[18] When two items are in tension or balance the relation of the two can shift in these three ways.

The idea of homeostasis is frequently invoked in clinical medicine and seems an almost inevitable explanation of changes in function and behavior. The most satisfying explanation for the vigor of the concept of homeostasis is that it is useful. The utility of the concept of homeostasis is seen in endocrinology, nutrition, cardiovascular and pulmonary diseases, autonomic physiology, and even in psychosomatic medicine and social science.

In addition to utility, it is possible to offer less exalted explanations of the vigor of homeostasis. Patterns of learning in childhood train humans in the concept. Fear, sickness, guilt, punishment, and success are related to an increase or decrease in forces a child contends with daily. In school sins of both omission and commission become important, and failure in good works is hazardous. Later the teenager lives in a climate of massive disequilibrium. As much as at any time in life, the teenager interprets his difficulty in terms of too much or too little in and around him.

Human concern for balance and stability may depend on deeper factors than cultural patterns and the conditioning of children. Life itself seems characterized by organization, at least a shifting order. A desire for solidity, constancy, and routine may be intrinsic in the human search for pleasure.

Part of man's evolutionary heritage is the need for an explanation for all major events and homeostasis serves as a convenient general answer. In a world largely beyond human control the idea of a theoretical golden mean has strong attraction.

The Disequilibrium Theory of Psychosis

If we assume that the real strength of the concept of homeostasis is utility, the concept should also be useful as a somatic explanation of psychiatric symptoms. It might be simplified as follows: The symptoms of psychiatric disease are associated with and may be produced by a change in activity of one portion of the CNS in relation to other areas. For example, either markedly decreased peripheral sensory input or markedly increased sensory input might produce a psychiatric disorder. Inability to integrate or absorb the sensory input could similarly produce disease. Neurochemical peculiarities, hereditary predispositions, or neurophysiologic patterns formed at a time of plasticity in the CNS could all distort the proper neurologic balance toward mental illness.

Other examples can be seen in the discussion of depression, anxiety, and hallucinations above. The general theme remains the same. Psychic states are produced by the relation of two or more functional neuronal areas, and a change of activity in any of the related areas can be associated with a shift in the psychic state. A change in activity of a particular area may be of prime importance, but is important only when change in the particular area shifts the balance between it and other areas.

Note: This material has been reviewed by the Office of the Surgeon General, Department of the Army, and there is no objection to its presentation

and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

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Recent Developments in Psychoanalytic Research

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(The first part of this article was published in the November, 1961, issue of *Diseases of the Nervous System.* This installment concludes the article.)

The Development of a Therapeutic Community at the Austen Riggs Center

Since 1952, two other staff members and I have been studying the development of a therapeutic community at the Austen Riggs Center. In this paper only a brief description of the institution and a summary of the main findings of our research are possible. The various aspects of the development of the Center have been described by Coon and Raymond (1940), Kubie (1960), and Knight (1960). The development of the therapeutic community at Riggs has been described by Polansky, Talbot, Miller, and myself in other publications.

The research has been largely clinical: the basic data have been comprehensive clinical notes about the development of the hospital social structure, including the minutes of all group meetings, committee reports, transcripts of staff conferences, etc. We have also used other, nonclinical, methods to measure attitudes of both patients and staff. These have included periodic interviews, questionnaires, sociometric charting (Polansky, Miller, and White, 1957), and the use of the semantic differential technique (Talbot, Miller, and White, 1961).

Austen Riggs is a small (42 in-patients), completely open, private psychiatric hospital in which psychoanalytically oriented psychotherapy is the basic mode of treatment. No shock therapy is done and drugs are used sparingly. All patients are seen in individual psychotherapy for about four hours each week. In addition, each patient par-

ticipates in a comprehensive program of group treatment. This program evolved from the dissatisfaction felt by patients and staff when treatment consisted almost solely of individual psychotherapy in a traditional hospital structure. After experimenting for a period with a relatively laissez-faire milieu, both patients and staff found a social vacuum as unsatisfactory a context for psychiatric treatment as the preceding authoritarian structure (White, Miller, and Polansky, 1955).

The present complex social structure of the hospital has evolved slowly over the past decade out of the kinds of dissatisfactions noted above. This evolution has been guided by one basic principle—that patients can and should participate to the greatest possible extent in the development and administration of policies and procedures that govern life in the hospital. Through this principle the institution has developed a social structure that accomplishes a number of separate but related therapeutic tasks:

1. To develop in the patient an understanding of how and why he behaves in an immature, self-defeating, and socially unproductive fashion, and to resolve the unconscious conflicts that cause and perpetuate his maladaptive behavior.
2. To counteract the regressive side effects of intensive individual psychotherapy.
3. To counteract the regressive side effects of living for extended periods in the sanctuary of the hospital community.
4. To help the patient regain the use of those capacities, talents, and abilities that were impaired by his illness, and, especially with the very young patient, to help him to develop new skills, talents, and abilities.

These tasks are accomplished through four programs of treatment: individual psychotherapy, a work program, a program of community government, and an educational program.

The development of insight and the resolution of intrapsychic unconscious conflict are primarily the task of the two-person interaction of individual psychotherapy. From the support of his relation with a trustworthy and skilled psychotherapist, the patient may gain sufficient hope, trust, and courage to face the worst in himself—those unconscious impulses that are infantile, greedy, hateful, destructively sexual, and that cause his anxiety and maladaptive behavior. By facing what he fears most in himself, he may master it. This is a painful and disturbing task. Often the patient's behavior becomes temporarily more infantile as he becomes absorbed in his efforts at self-scrutiny and self-understanding. As his conflicts become more clearly focused in his awareness, his tension and his disturbed behavior may increase. These are some of the regressive side effects of individual psychotherapy.

If life in the hospital community presents him with few demands for adult behavior and with few consequences if he behaves in a socially disruptive and infantile manner, the patient may be greatly tempted to make a career of his neurosis. Burnham (1961), from observations at Chestnut Lodge, has noted the same point. Such patients tend to band together in a mutually protective alliance, saying, in effect, "we are all disturbed and none of us must criticize another's neurosis or expect him to change." These are some of the regressive side effects of living for extended periods in the sanctuary of the hospital.

In order to counteract such side effects, the patient must be provided with, among other things, day-to-day genuine responsibilities for himself, for other patients, and for the institution in which he is a temporary citizen. To provide these responsibilities, the hospital social structure must make available to the patient roles other than the traditional role of sick person in treatment—specific social roles through which he participates in the hospital community in a number of ways.

At Riggs all patients participate in weekly meetings of small groups that form the basic administrative units of the hospital. Each group contains about ten patients, one or two nurses, and a member of the psychotherapy staff (either a psychiatrist or a psychologist). These groups serve as forums for discussing issues of group life, as units for electing patient representatives to the

three major committees that largely govern the hospital, and as a means for introducing new patients.

The three major executive committees of the institution are composed of about six elected patients and two or three representatives from the psychotherapy, nursing, teaching, or maintenance staffs. These committees are responsible for a great deal of the routine administration. One of these committees concentrates on evolving and administering the rules and laws of the community—regulations that govern such matters as the use of alcohol among patients, the assignment of rooms to patients, the control of noise or other troublesome behavior. A second committee conducts a work program in which each patient participates daily. The money saved by the work, amounting to more than $10,000 a year, is credited to a free care fund that helps needy patients to finance treatment. The work performed ranges from scrubbing floors to building furniture for the rooms occupied by patients. The third committee, in collaboration with the teaching staff, helps to plan and conduct a program of education and recreation for patients. This program resembles adult education and offers the patient a wider and more stimulating range of subjects than is offered by traditional occupational therapy. Included in the program are drama production, operation of a nursery school for children of the town, typing lessons, current events seminars, woodworking, furniture refinishing and so on.

Every other week the staff, including nurses, teachers, some business office personnel, some maintenance and service personnel, psychologists, and psychiatrists, meet to discuss matters of concern to the staff. On alternate weeks all staff and all patients participate in a community meeting to discuss issues of concern to the entire community, both patients and staff. Once or twice a month all patients meet with a few staff members to take up questions that primarily concern the patients.

By means of this rather complex community structure, patients are provided with a variety of social roles. In addition to their traditional and more passive social role of psychologically disturbed patients in treatment, they have the more active roles of workers in the work program, citizens in the hospital community, and students in an educational program. These various roles and the social structure I have described offer the patient an active and respected voice in, and real responsibility for, the operation of the community in which he temporarily resides. This multiple set of roles for the patient contrasts greatly with the usual single role provided for the hospitalized patient—the role of passive guest-inmate.

Our experience shows that without the opportunity and stimulation of active roles, hospitalized patients tend to regress excessively, and even skilled psychotherapy may be ineffective when conducted in a social vacuum. If patients are to be provided with active roles, the staff must be willing to relinquish many of its time-honored authoritarian prerogatives. Patients will question and provoke the staff in the most fiendishly ingenious ways to test whether the role of active participants held out to them is real or only the sham so characteristic of student governments—namely, "you may have a voice in deciding things so long as you decide them in the way that we, the faculty, want them to be decided."

Individual therapy can foster insight and help the patient to resolve those anxieties and conflicts which perpetuate his neurosis, but to only a limited degree can it provide the conditions necessary for him to exercise those skills, abilities, and talents that remain intact, to restore those that have been lost by illness, or to develop new ones. Individual psychotherapy may free him from his inhibitions, but it cannot teach him to dance, play bridge, speak French, or use a typewriter. If the society of the hospital grants the patient the opportunity to learn by being a citizen of the hospital community, it will surely improve his ability to rejoin society at large upon his discharge, but even this is often not enough. For example, an inhibited young person who has broken down in his early years of college, may never have developed many of the basic

social skills or any of his manual, intellectual, or creative potentialities. If a young person must be hospitalized for one, two, or three years, as some of the more seriously disturbed must be, it is crucial that the development of his social, intellectual, and other skills not be put in mothballs. The hospital should provide opportunities for continued education, especially for the younger patients who have had to abandon their careers as students. The hospital should also acquaint or reacquaint its patients with meaningful work, an opportunity rarely extended to patients, especially those in private hospitals.

Our observations about the influence of the social structure and atmosphere of the hospital on the patient's psychic conflicts support a number of psychoanalytic concepts, especially Rapaport's (1951, 1958) concept of ego autonomy and Erikson's (1950) concept of the psychosocial stages of ego development.

Specifically, our findings support Rapaport's claim that the integrity of the ego depends in large measure on an adequate input of appropriate "stimulus nutriment" from the environment. To Rapaport's formulation we would add that the kind and amount of stimulus nutriment available to an individual are governed by the kind and number of social roles available to him. We have seen patients regress excessively so long as the staff considered the hospital more or less as a repository to contain patients between psychotherapy hours. Conversely we have seen nearly psychotic patients retain their sanity largely through the opportunities, demands, and responsibilities placed on them as they filled the social roles of worker, citizen, and student in the hospital community.

Although the situation that we have studied was devoid of those gross failings characteristic of state hospitals, our experience suggests that mere avoidance of such gross evils is insufficient. If the institution is in fact to be a therapeutic community, it must provide social roles that impose significant but not excessive social demand and expectation, and roles that provide educational opportunities. It must also provide the social role of sick person which grants sanctuary.

Space does not allow an extensive discussion of the relevance of the therapeutic community to Erikson's concept of the psychosocial stages of ego development. I will mention only that, during their hospital stay, patients tend to recapitulate the various developmental crises of the ego—especially those of trust versus mistrust, autonomy versus shame and doubt, initiative versus guilt, and identity versus identity diffusion. When the great majority of patients are late adolescents or very young adults, as they are at Riggs, the successful resolution or recapitulation of the identity crisis is of special importance. Unless such a patient is provided with a variety of roles, such as worker, student, citizen, that prepare him to return to life outside, he is likely to crystallize a permanent identity that suits him only for a career that has little to recommend it: that of psychiatric patient.

Experiments on Subliminal Perception

Recent experiments on subliminal or incidental perception have brought rigorous laboratory methods to bear on a number of abstract psychoanalytic concepts that, until now, have been derived from and supported almost solely by clinical data. Klein (1959 a, 1959 b), Klein and Holt (1960), Pine (1960), and others, have explored the implications of these experiments for such issues of psychoanalytic theory as the differences between primary- and secondary-process thought, the nature and function of the day residue in dream formation, the psychoanalytic assumptions about the nature of consciousness, and the relation of instinctual drives to processes of perception. In this paper I will emphasize the particular relevance of these experiments for psychoanalytic technique, an area as yet unexplored except for the preliminary and generally inadequate speculations of Tauber and Green (1959).

The results of experiments on subliminal

perception by Fisher and Paul (1959), Klein, et al. (1958), and others, can be summarized as follows: a visual stimulus, for example, a picture, or a word, is flashed on a screen for a fraction of a second, too briefly to be consciously perceived. Although the subject has no conscious awareness of what was flashed on the screen, the subliminal stimulus may, nonetheless, later appear in or significantly influence his thoughts, spontaneous imagery, and dreams. Usually the subliminally perceived stimulus does not appear directly in subsequent thought; it appears only in a somewhat altered or derivative form. For example, after the words SMOKING—GOOD were presented subliminally, direct references to smoking did not appear in the spontaneous imagery of the subjects, but oral imagery (eating, drinking, sucking, etc.) was prominent, more so among smokers than nonsmokers. In another experiment, when the word ANGRY was subliminally flashed on a screen and was then followed by an emotionally neutral picture of a human face shown long enough to be clearly perceived, the face tended to be seen as more unpleasant than when HAPPY was used as the subliminal stimulus.

We are assured by Klein (1959 b) that we are not in danger of being subliminally brainwashed into smoking a particular kind of cigarette or of changing our brand of beer as we watch the late late show on television. Subliminal or incidental stimuli have little effect on the reality-oriented, problem-solving, logical thinking with which we run the practical affairs of our lives. Subliminal stimuli tend to influence our thoughts most when we give ourselves over to reverie, when we relax and allow our thoughts to wander, and when we dream; that is to say, subliminal stimuli have a greater impact on our illogical or primary-process modes of thought than on our focused, logical thought.

The greater influence of subliminal and incidental stimuli when we relax and allow our thoughts to wander freely is of considerable importance for psychoanalytic technique. Psychoanalytic training has long stressed the importance of the therapist's assuming an attitude of relaxed free-floating attention rather than an attitude of deliberate and effortful attentiveness. Other than Freud (1912), only Reik (1948) has seriously considered the importance of this attitude of free-floating attention and its relation to the analyst's ability to receive and recognize subliminal or incidental stimuli from his patient. Reik, like Freud, based his study on clinical evidence only.

Fifty years ago Freud described the attitude that the analyst should assume as he listens to his patient. His recommendations are as sound today as they were in 1912:

"The technique is a very simple one. It . . . simply consists in making no effort to concentrate the attention on anything in particular, and in maintaining in regard to all that one hears the same measure of calm, quiet attentiveness—of 'evenly-hovering attention,' as I once before described it. In this way a . . . danger inseparable from deliberate attentiveness [is] avoided. For as soon as attention is deliberately concentrated in a certain degree, one begins to select from the material before one; . . . and in this selection one's expectations or one's inclinations will be followed. This is just what must not be done, however; if one's expectations are followed in this selection there is the danger of never finding anything but what is already known, and if one follows one's inclinations anything which is to be perceived will most certainly be falsified" (p. 324).

"What one achieves in this way will be sufficient for all requirements during the treatment. Those elements of the material which have a connection with one another will be at the conscious disposal of the physician; the rest, as yet unconnected, chaotic and indistinguishable, seems at first to disappear, but rises readily into recollection as soon as the patient brings something further to which it is related, [but] . . . a conscious effort to retain a recollection of the point would probably have resulted in nothing" (p. 325).

"All these rules . . . aim at creating for

the physician a complement to the 'fundamental rule of psychoanalysis' for the patient. Just as the patient must relate all that self-observation can detect, and must restrain all the logical and affective objections which would urge him to select, so the physician must put himself in a position to use all that is told him for the purposes of interpretation and recognition of what is hidden in the unconscious, without substituting a censorship of his own for the selection which the patient foregoes. Expressed in a formula, he must bend his own unconscious like a receptive organ toward the emerging unconscious of the patient, be as the receiver of the telephone to the disc. As the receiver transmutes the electric vibrations induced by the sound-waves back again into sound-waves, so is the physician's unconscious mind able to reconstruct the patient's unconscious, which has directed his associations, from the communications derived from it" (p. 328).

The support for Freud's proposals that can be derived from experiments on subliminal perception is obvious, and the more important if one keeps in mind a notable characteristic of the psychiatric patient: his tendency to reveal the central issues of his neurosis to his therapist only gradually and in disguised form. For long periods he gives only small hints and veiled indications of his pathogenic unconscious impulses—a fleeting gesture, a brief change of facial expression, a tone of voice, a dream. These clues are usually incidental or peripheral to the main topic of his conversation. If the therapist strained to understand the overt utterances of the patient he would probably miss completely these crucial, although covert, incidental, even subliminal, communications. Accrued psychiatric knowledge and these recent experiments on subliminal perception indicate that the therapist is in error if he deliberately and effortfully concentrates on what the patient is saying. If he does so, he will be less receptive to those important peripheral or subliminal cues from his patient, and furthermore, those incidental cues that he has unconsciously perceived will be less likely to float up into his conscious awareness.

Here is a clinical example of the way in which incidental stimuli from a patient may be registered outside of awareness and then come into the awareness of the therapist as spontaneous imagery:

On a rather warm day a patient was rambling on about matters that seemed of little importance. As he droned on, I felt rather drowsy and my thoughts began to wander. Suddenly I began to have the vivid and rather surprising fantasy that the patient had leaped from the couch and was attacking me. I brushed the fantasy aside with the thought that I really must attend to the patient's problems and leave my own to be pondered later. But soon the same fantasy returned more vividly and compellingly. Deciding that it might tell me something about my patient's worries as well as my own, I gave the imagery free rein. In the daydream I struggled with the patient, but I was soon overpowered. His hands closed about my neck. I gave a last choking gasp. I knew I was a goner. Just at that moment my attention was suddenly and forcefully drawn back to my patient's actual behavior. He had become extremely quiet. Gripped by the fantasy, I also had become very quiet. The room was in fact as still as death. At that point the patient burst into tears, abruptly sat up, and turned to look at me with horror and fear in his face. "My God!" he said, "I had the most frightening thought—I thought that you had just died. I listened to try to hear you breathe but I couldn't. I became convinced that you had died."

Needless to say, the patient's sudden movement startled me considerably. What is important, however, is that very subtle cues from him, cues of which I was not aware, had registered and had then come into my consciousness in the form of a fantasy of a murderous attack. Among these cues, as I later realized, were a fleeting expression of rage on his face as he entered the office and a few angry overtones in his manner of speech. Had I been effortfully trying to follow the exact meaning of his

obsessional meanderings, I doubt that these peripheral cues would have registered in my unconscious and have given rise to my subsequent fantasy. I doubt that the room would have become so still as to make him fear that I had died. As a result of the events of this hour, we were able to explore fruitfully his very primitive, murderous impulses toward men, including myself. His compulsive calmness and detached attitude were broken through. Genuine affects of anger, fear, and guilt came into his conscious awareness for the first time.

Dream Deprivation

In a series of experiments, Dement (1955, 1957 a, 1957 b, 1958) found changes in the electroencephalogram and in eye movements that occur only when a sleeping person is dreaming. By awakening the person as soon as the brain waves and eye movements indicate a dream has started, dreaming can be almost completely prevented. Dement (1960) has recently reported an experiment in which eight normal subjects were prevented from dreaming for as many as seven consecutive nights. Despite several awakenings each night, each subject slept the same number of hours that had been established as characteristic for him. All subjects developed significant psychological disturbances when prevented from dreaming. All developed anxiety, irritability, and difficulty in concentrating. One subject suffered "serious anxiety and agitation." One quit the experiment in a state of near panic, and two others insisted on stopping short of the prescribed goal of at least five nights of dream deprivation. All subjects returned to normal as soon as they were allowed to dream. In the several nights following dream deprivation, all subject caught up on their dreaming, dream time jumping from a mean of 82 minutes per night to 127 minutes per night. This process of catching up continued for as long as four nights. Dement concludes, "it is possible that if dream suppression were carried on long enough a serious disruption of personality would result."

Psychoanalytic theory assumes that instinctual drives, sexual and aggressive, find partial discharge in fantasy during dreaming. A common example of the discharge of instinctual drive, not a very satisfactory discharge to be sure, but better than none, is the sexual dream with orgasm. Psychoanalytic theory also assumes that our psychic well-being is threatened and anxiety results if unacceptable instinctual impulses become too intense. If dreaming is a kind of safety valve for the expression of disturbing instinctual impulses, then psychological disturbances should result if this outlet is denied to the sleeper. This is exactly what Dement's ingenious experiment shows, though of course it only supports and by no means proves those aspects of psychoanalytic theory to which I have referred.

Summary

I have tried to give a view of current research on psychoanalytic therapy or research that is relevant to psychoanalytic theory or therapy. The need for more well-designed studies to explore, refine, and alter psychoanalytic theory and methods of treatment is clear. Better understanding of the human psyche and better means of producing therapeutically desirable changes in it are hard to come by. In the face of this formidable task it may be heartening to remind ourselves that our colleagues in other branches of medicine, whom we sometimes assume have more reliable methods of treatment and diagnosis, may not be so far ahead of us as we tend, in moments of uncertainty, to suppose. Kline (1961) helps us to keep good spirits about our predicament by referring to an experiment done some years ago. This experiment was an attempt to determine the validity and reliability of the judgment of physicians about the relatively simple question whether a child should have a tonsilectomy. One thousand school children were surveyed. Of these 61% had already had their tonsils removed. The remaining 390 were examined by a group of physicians and 174 were considered in need of tonsilectomy. The remaining 215, who were considered healthy, were then re-examined by a second panel of physicians, and tonsilectomy was recommended for 99. When

the remaining 116 children with supposedly normal tonsils were examined by a third panel, another 51 were found to need tonsilectomy. After three examinations only 65 children remained who had not yet been diagnosed as needing tonsilectomy. The experiment was stopped at that point because the supply of examining physicians ran out.

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Psychosomatic Aspects of Hyperadrenocorticism Treated with Chlorpromazine

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The term "hyperadrenocorticism" refers to increased adrenal cortical hormone production which is associated with a variety of clinical conditions, including adrenal cortical tumors, basophilic adenomas of the pituitary, "primary" adrenal cortical hyperplasia, and physical or emotional stress.

Although there have been many studies of effects of psychologic stress on adrenal cortical functioning, only one study[1] was found which reported the urinary adrenal steroid excretory levels of a group of anxious subjects. This is surprising since the 24-hour urinary determination is generally felt to be the most accurate method of measuring adrenal steroid production.

While a fairly extensive literature exists concerning the effects of chlorpromazine on adrenal cortical function, an intensive review of this literature failed to reveal a single report of a case of hyperadrenocorticism in which chlorpromazine had been administered. The following presentation summarizes the psychiatric and laboratory findings and their interrelationships, in a case of hyperadrenocorticism with marked anxiety treated with chlorpromazine.

Case Report

The patient, a 42-year-old mother of four children, entered the hospital in June 1956, complaining of progressively deepening feelings of depression and mounting anxiety. She spoke of suicide and indicated that she had a serious problem with alcohol. This was her first admission to a mental hospital. Because of her increasing anxiety and "tension," which she prophetically attributed to a "glandular imbalance," the patient had consulted several physicians during the months immediately preceding her hospitalization. One of these physicians noted that the patient consumed inordinate amounts of water, and on the basis of this polydypsia, and concomitant polyuria, urinary adrenal steroid levels were determined and found to be elevated.

A general physical examination at the time of admission was not remarkable, revealing none of the usual signs of Cushing's syndrome. Blood pressure was 130/90 and a routine urine analysis and CBC were within normal limits. The fasting blood sugar was 75 mg.%, and the protein bound iodine and I^{131} uptake within normal limits, as were the serum sodium, chloride, potassium, and calcium, and CO_2 combining power. The total circulating eosinophile count was 55/cu. mm.

The patient was born in 1914, the youngest of six children, two boys and four girls. Her father was a taciturn, austere, emotionally detached college professor who devoted his life to intellectual pursuits, and spent little time with his family. The mother was a charming and gregarious but "high-strung" woman who suffered a "nervous breakdown" some months after the patient's birth. A college graduate at a time when few women had achieved this status, the mother was intensely interested in intellectual matters and imbued her daughter with a desire to excell intellectually. The mother's relationship with the patient was friendly but somewhat superficial.

The oldest sister, 11 years her senior, was a brilliant student and a strong-willed, aggressive girl who dominated her more dependent younger sister. After graduation from college this sister attained considerable recognition in her profession. Thus the patient grew up in the shadow of her oldest sister, and although the patient was also an excellent student, she never received the acclaim accorded her sibling. The patient's only brother, who was seven years her senior, left home to attend school while the patient was a young child, and there has been little contact between them. He is a university professor. The patient's closest relationship was with a warm and affectionate sister, three years her senior. This sister was divorced several years ago, and works as a school teacher. Two of the patient's siblings died prior to her birth.

During the patient's childhood and adolescence, the family moved about a good deal so that she rarely spent more than two years in the same school. Nevertheless, she did well scholastically, and graduated near the top of both her high school and university classes.

Following graduation, the patient worked in an administrative position until her marriage at age 24. The patient's husband was a brilliant, gregarious extrovert, the only son of an immigrant Jewish family. At the time of the marriage he held an academic position. The patient was Protestant and she and her husband differed greatly in character structure, values, and family and religious back-

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This study was done while the senior author was a psychiatric resident at High Point Hospital, Port Chester, New York.

ground. The early years of their marriage were relatively satisfying to both but the passage of time brought increasing amount of conflict.

In 1939 the couple's first son was born. The following year they had a daughter, and in the subsequent six years they had a second son and daughter. When the children were infants she devoted herself untiringly to their care, and was happier and less tense at these times. As the children grew older she felt less able to empathize and communicate with them and consequently found her role as a mother less satisfying. Because of her increasing interpersonal difficulties, the patient began psychoanalytic treatment in 1942 and continued until the family moved to another city three years later.

The patient was dependent upon her mother for emotional support during the increasingly frequent periods of marital conflict, and following her mother's death in 1948, the patient's psychiatric symptoms gradually became more marked. She had more frequent and prolonged periods of depression and she became more irritable and anxious. She also began to rely more heavily on alcohol.

The patient's relationship with her husband became increasingly strained, and in 1952 they separated. Following the separation, the patient became markedly depressed and began drinking heavily. The couple had a reconciliation two years later, "for the sake of the children," but the relationship was no more peaceful than before, and the couple were once again on the verge of separation just prior to the patient's hospitalization. When the patient told her husband that her condition had been diagnosed as "adrenal cortical hyperplasia," and attributed all her mental symptoms to this condition, talk of separation ceased.

For many years the patient had exhibited ambivalent feelings toward her body. On the one hand she was very fearful of physical injury or disease and hypochondriacally preoccupied with bodily functioning, and on the other she longed for a physical illness as "a way out." Her concern with her body was fostered by her family who had regarded her as a "cute china doll" during her childhood, and had paid more attention to her dress and personal appearance than they had with the older children.

Another factor contributing to the patient's somatic preoccupation is found in her medical history. During infancy she suffered from rickets, and as a consequence received much attention from her mother. The patient had the usual childhood diseases and at 16 had a tonsillectomy. She had an appendectomy in 1938, a severe case of pneumonia later that year, a subtotal thyroidectomy for colloid goiter in 1945, a venous stripping for varicosities of the lower extremities in 1946, menorrhagia for several years, and episodes of tachycardia beginning in 1955. In addition, the patient's infantile rickets resulted in pelvic dystocia which necessitated caesarean deliveries of all of the patient's children. During the months preceding her hospitalization, the patient's many somatic complaints multiplied.

Shortly after admission to the hospital in June, 1956, the patient was started on chlorpromazine 50 mg. q.i.d., gradually increased to 150 mg. q.i.d. by July 12, 1956. She remained on this dosage of chlorpromazine until October 1, 1956.

The patient's hospital course was greatly influenced by the vicissitudes of her relationship with her husband. At the time of her admission the patient was unsure of her husband's feelings toward her. After the patient's condition had been diagnosed "adrenal cortical hyperplasia" the husband dropped his plans for separation, and became more thoughtful and sympathetic toward the patient. He gave every indication that he planned to continue their marriage following her discharge from the hospital. The patient suspected however, that her husband did not basically love her, and attributed his recent change of heart to a sense of duty. She also feared that he would be unable, or unwilling, to continue his present exemplary behavior over any prolonged period. She felt trapped, in that she would not consider a separation from her husband, nor could she contemplate returning to the type of marital relationship that had existed during the past few years.

Following her hospitalization, the patient gradually became less depressed and somewhat less anxious. Although she continued to suffer from anxiety, "tension," and periods of depression, these symptoms were less severe than those she experienced prior to hospitalization.

The initial hospital visits with the husband were relatively harmonious, but as the patient's hospitalization progressed, the couple frequently quarrelled, and it became increasingly apparent that the patient would not be able to adjust to the marriage. The patient herself had many doubts concerning her marriage, and often asked her therapist if he felt the marriage could survive. By the patient's third month of hospitalization it was relatively evident that the marriage would be no more satisfactory in the future than it had been in the past, and at this time the therapist conveyed this impression to the patient. Her immediate response was, "I guess I wanted you to tell me that, didn't I?" During the next few weeks the patient continued to visit with her husband, but gradually decided to separate from him. She became progressively more depressed following this decision, and because of the suicidal risk, a series of electric shock treatments was recommended. The patient's chlorpromazine was gradually discontinued between October 1 and October 5, 1956. Between October 6 and October 18, 1956, the patient received six EST's, which greatly relieved her depression. For the first time during her hospitalization the patient was able to make future plans for herself which did not include the husband, and she began to look for an apart-

ment in preparation for her discharge from the hospital.

During the remaining weeks of her hospitalization, the patient again became depressed and complained of "tension," but these symptoms were much less marked than they had been prior to EST. The patient had entered the hospital on a voluntary basis and several weeks after the completion of her EST she left the hospital against the advice of the medical staff.

Post-Hospital Course

Within a few weeks after leaving the hospital the patient became seriously depressed, and on February 3, 1957 attempted suicide which led to her commitment to another hospital.

During the preceding three months determinations had been performed in three different laboratories on four separate 24-hour urine specimens, the total volumes averaging 6700 ml., with a range of 5200 to 8800 ml. These specimens showed a mean 17-ketosteroid excretion of 15.5 mg., with a range of 10.3 mg. to 17.6 mg. (normal 6-15 mg.), and a mean 17-hydroxycorticosteroid (17-OHCS) excretion of 27.3 mg., with a range of 13.7 mg. to 48.4 mg. (normal 3-10 mg.). In April 1956, one 24-hour urinary 11-oxysteroid determination was 28.6 mg. (normal 1.0 to 2.5 mg.).

Following 25 units of ACTH intravenously the 24-hour urinary 17-ketosteroid excretion was 41.0 mg. (normals averaged 15.4 mg.[2]), and the 24-hour 17-OHCS excretion was 52.5 mg. (normals averaged 21.0 mg.[55]). These levels are similar to excretory patterns seen in adrenal cortical hyperplasia.

On June 26, 1956, the patient was placed on chlorpromazine, 50 mg. q.i.d., and this was gradually increased to 150 mg. q.i.d. by July 12, 1956.

Between August 12 and October 2, 1956, determinations on six 24-hour urine specimens, the total volumes ranging from 1775 mg. to 3850 ml. (mean, 2760 ml.), showed a mean urinary 17-ketosteroid excretion of 10.2 mg. (range, 8.1 mg. to 12.7 mg.) and a mean 17-OHCS excretion of 10.2 mg. (range 7.9 mg. to 12.6 mg.).

The difference between the mean of the 17-ketosteroid excretion values before chlorpromazine was administered (15.5 mg.), and that after chlorpromazine was instituted (10.2) is significant at the 0.01 level using the t-test. The difference between the means of the urinary volumes, and the means of the 17-OHCS excretions values before and after chlorpromazine are significant at better than the 0.005 level.

On October 27-29, 1956, following completion of the series of EST two 24-hour urine specimens (volumes, 2850 ml. and 2000 ml.) revealed 17-ketosteroid excretion levels of 10.4 and 11.7 mg., and 17-OHCS levels of 14.2 and 14.5 mg. On December 15-16, 1956, the patient's 24-hour urinary 17-ketosteroid excretion of 14.8 mg. Creatinine determinations done on all the above 24-hour urine specimens indicate that complete collections were obtained.

On February 20, 1957, following the patient's admission to another mental hospital, the 24-hour urinary 17-ketosteroid excretion was 14.4 mg.

Table I presents a summary of this data.

TABLE I

Steroid Values and Urinary Volumes

Time of Determinations	24-hour 17-ketosteroid (normal, 6-8 mg.)	24-hour 17-OHCS (normal, 3-10 mg.)	24-hour urinary volume
Prior to chlorpromazine administration, April-May 1956 (Av. of 4 separate determinations)	15.5	27.3	6700
During chlorpromazine administration, August-October 2 (Av. of 6 separate determinations)	10.2	10.2	2760
3 weeks after the termination of chlorpromazine, Oct. 27-29 (Av. of 2 separate determinations)	11.1	14.3	2435
2-4½ months after termination of chlorpromazine, December 15, '56, and February 20, 1957 (Av. of 2 separate determinations)	14.6	not determined	3710

Review of the Literature and Theoretical Considerations

The experimental literature concerning the effects of chlorpromazine on adrenal cortical function presents a confusing picture. A comparison of the results of different investigators is difficult because no two studies are identical in terms of dosage of the drug, mode of administration, type of experimental animals, and the period elapsing between the administration of the chlorpromazine and the measurement of its effect. Using adrenal cortical ascorbic acid depletion as a measure of secretory activity, several investigators[4-8] found that in rats chlorpromazine inhibited the usual cortical response to various physical stresses, such as surgery or large doses of epinephrine. However, other authors[9,10] found that chlorpromazine not only failed to inhibit adrenal cortical ascorbic acid depletion of stress, but following injection actually produced adrenal ascorbic acid depletion when compared with saline. Both of the latter investigators used chlorpromazine dosages in the range of 1 mg./100 gm. of body weight or below, and Sevy[8] reports that in

his investigations dosages in this range failed to protect against adrenal ascorbic acid depletion following stress, whereas higher dosages did. Confirming the finding that chlorpromazine can act as stimulant to the hypothalamic-pituitary-adrenal cortical system, Egdahl, et al.[11] found that the compound given intravenously increased the adrenal venous 17-OHCS in unanesthetized dogs. Harwood, et al.,[12] demonstrated that chlorpromazine in low doses given intravenously to monkeys produced an increase in blood 17-OHCS, whereas high doses did not produce this result. It is believed that chlorpromazine acts through the hypothalamic-pituitary system rather than on the adrenal cortex directly since large doses of chlorpromazine produce no inhibition of the adrenal cortical response to exogenous ACTH,[7,8] and the increased production of adrenal steroids produced by intravenous chlorpromazine was abolished by hypophysectomy.[11] The finding that chlorpromazine in high doses stimulates electrical activity in the reticular formation, and depresses this activity in low doses[13] may be related to the above findings.

There have been relatively few studies of the effect of chlorpromazine on human adrenal steroid metabolism. Christy, et al.[14] found chlorpromazine administration (100-400 mg.) two hours prior to insulin coma therapy prevented the usual increase in plasma 17-OHCS. However, other authors[15] found no indication that chlorpromazine (50-175 mg.) inhibited adrenal cortical response to surgical stress in humans. The discrepancy in these results can probably be accounted for in the lower dosage used by the latter investigators. Following daily chlorpromazine administration to three female patients, 24-hour urinary 17-ketosteroid excretion was found to fall from normal values to values near zero within 18 days, and then gradually return to normal despite continuation of the chlorpromazine, whereas only insignificant decreases in the 24-hour urinary 17-OHCS levels were obtained.[16]

While it has been demonstrated that reserpine prevents the increase in plasma 17-OHCS which ordinarily followed the presentation of a "fear" provoking conditioned stimulus to monkeys,[17] no studies were found which dealt with the effects of chlorpromazine on the usual increase in plasma adrenal steroids following psychological stress.

That psychological stresses of various types can activate increased production of adrenal steroids has been demonstrated repeatedly.[1,18-22] Anxious patients have been found to have higher urinary and plasma levels of adrenal steroids than normals;[18] 24-hour urinary 17-OHCS determinations of 16 anxious patients revealed a mean value of 8.04 mg., with a standard deviation of 5.20 mg., as compared with a mean of 4.77 g. (S.D. of 2.38) for 16 "normal" controls.[1] Further studies[23,24] demonstrated that these elevated plasma and urinary hydrocorticoid levels were due to an increased rate of production of hydrocortisone, and were not accounted for by a diminished rate of disposal of the hormone. The rate of disappearance of hydrocortisone from the plasma of anxious subjects was actually significantly faster than in normal subjects.[24]

There has been a great deal of speculation concerning the relationship between adrenocortical functioning and mental processes, and the problem has been approached from many points of view. Addison[25] in his description of the syndrome occurring in patients with deficient adrenal steroid production, mentioned the psychological symptoms which are usually associated with this disorder, and most clinical descriptions of the illness written since his time have noted the greatly variable nervous and mental aspects of the disease. Wallerstein, et al.[26] in an extensive presentation of the psychosomatic aspects of Addison's disease report on a series of 25 patients suffering from both Addison's disease and psychosis, and discuss various theories pertaining to hypofunction of the adrenal cortex and mental illness.

Psychiatric symptoms are also frequently reported associated with hyperfunction of the adrenal cortex. Plotz, et al.,[27] in a review covering 222 cases of Cushing's syndrome report that 49% of these patients had mental symptoms such as anxiety, tension, emotional lability, irritability, insomnia, de-

pression, hallucinations and delusions; and that 24% of a smaller group (33 patients) seen at Presbyterian Hospital in New York City developed psychoses or neuroses severe enough to require hospitalization. The administration of cortisone or ACTH to patients suffering from a variety of nonpsychiatric conditions has been associated with the appearance of similar symptoms, and occasionally psychoses have developed.[28-30] Affective psychoses, conditions resembling toxic psychoses, and schizophrenic-like responses have been reported.

An experimental approach to the relationship between schizophrenia and adrenal cortical functioning was made by Pincus, Hoagland, and their associates, who found that schizophrenic patients had a defective adrenal cortical response to either ACTH, or a number of standard experimental stresses.[31-34] These studies led some investigators to believe that the adrenal cortex might play an important part in the etiology of schizophrenia, and it was hypothesized that adrenalectomy might produce beneficial results in schizophrenic patients. However, a recent six-year follow-up study of eight schizophrenic patients on whom bilateral adrenalectomies had been performed did not support this hypothesis.[35]

From the data summarized above it would appear that similar symptoms may occur following either a deficiency or an excess of adrenal steroids, and it is one of the puzzling aspects of adrenal metabolism that the same steroid may have seemingly opposite effects, for example, on one occasion stimulating water retention, and on another promoting diuresis.[36]

Discussion

In testing a therapeutic method one cannot draw definite conclusions on the basis of a single case; however, one can form clinical impressions from the intensive study of a single patient, especially when the data is consistent with experimental evidence as it is in the present case. The patient's excretion of adrenal steroids decreased following admission to the hospital. Evaluation of the various aspects of her treatment situation is necessary in order to establish a clinical impression concerning the factors involved in the observed reduction. Possibly some unknown factor led to the reduction. However, before accepting such a hypothesis the more apparent elements involved should be examined.

One commonly observes a reduction in anxiety and of other psychiatric symptoms following hospitalization, even if no specific treatment is given. The present case showed a moderate symptomatic improvement shortly after admission in June but during September she was extremely depressed and "tense" despite continued hospitalization. One would assume that if the decrease in steroids resulted from a reduction in depression and anxiety as a consequence of hospitalization, the steroids would have risen when the patient again became disturbed, but the steroid values for September did not differ from those obtained in August. The failure of the patient's increased depression and anxiety to produce a concomitant increase in adrenal steroids may be due to chlorpromazine's action as a "hypothalamic blocking agent," the drug thus reducing the cerebral cortex's influence on the hypothalamic-pituitary system.

Harris[37] notes that phenobarbital tends to lower 17-OHCS levels, and the patient received phenobarbital, one grain three times daily, from September 2 to her discharge. However, this medication could not account for the fall in the patient's steroids during August, nor did it prevent the increase in the patient's 17-OHCS in October, and hence it does not appear likely that the observed variations in her corticoids were due to phenobarbital.

It is difficult to evaluate the effects of psychotherapy on the patient's adrenal steroids, but presumably any effect would be brought about through a reduction in the patient's depression and anxiety, or through some change in the patient's defenses or personality structure. That the reduction in the patient's psychiatric symptoms was not constant during the period when her adrenal steroids were consistently reduced (August-September) was discussed above. Psycho-

therapy was primarily supportive and brought about no apparent change in the patient's personality structure or defenses, other than strengthening the latter.

The increase in the patient's steroids following the discontinuation of chlorpromazine is not marked, but it is in the expected direction if we assume chlorpromazine was responsible for the decrease in her steroids. However, the EST the patient received also has to be considered. Bliss, et al.,[38] demonstrated that while EST elevated the plasma 17-OHCS, these steroid levels returned to normal within four hours after the treatment was given. Since the patient received her last EST on October 18, and the urine specimens were collected on October 27, 1956, through February 20, 1957, it seems unlikely that the EST was a contributing factor in the elevation of her 17-OHCS.

From the evidence given above, chlorpromazine would appear to be the agent primarily responsible for the observed reduction in the patient's steroid levels. The validity of this assumption is strengthened by the fact that it is in accord with the experimental evidence cited.

The patient's polydipsia and polyuria present interesting psychosomatic problems. Over 30 per cent of patients with Cushing's syndrome develop polyuria and polydipsia.[27] These symptoms have been attributed to the tendency of some adrenal corticoids to oppose the action of the posterior pituitary antidiuretic hormone and to changes exerted on sodium and potassium metabolism.[39] The patient's polydipsia could therefore be attributed to her elevated adrenocorticoids. However, another hypothesis is possible. The patient had drunk alcohol for many years and was an orally dependent person. On card VII of the Rorschach she saw "donuts," "fried shrimp," and "two gingerbread men dancing." On card VIII she saw "breasts," and in another area, "ice cream cones." She reported to her therapist that most of her pleasant early memories were associated with water. During her hospitalization she also noticed a tendency to drink more water when she was "tense and nervous." The patient's polyuria could therefore be attributed to an excessive fluid intake resulting from repressed oral needs. With the data available it is impossible to adequately evaluate this possibility. However, the patient's fluid intake did not increase during the period she was receiving chlorpromazine, despite the fact that her anxiety increased considerably during September. This lends support to the hypothesis that the patient's elevated steroids played the more important role in her polydipsia.

Our case raises several questions about the nature of Cushing's syndrome. Prior to the administration of chlorpromazine, the patient's adrenocortical steroid levels were higher than those found in many cases of Cushing's syndrome. Plotz, et al.,[27] report that in 25 patients with Cushing's syndrome, the 24-hour urinary 17-ketosteroids averaged 12.2 mg. (range 0-26.6 mg.) and in six patients the 24-hour urinary 11-oxysteroids (formaldehydogenic method) averaged 3.87 mg., with a range of 0.86 mg. to 6.3 mg. (normal 0.5-1.5 mg.) Apparently some individuals with steroid levels close to "normal" develop Cushing's syndrome, and others, such as our patient, do not develop the syndrome although their steroid values are far in excess of "normal," and exceed the average values found in patients with Cushing's disease. This problem is exemplified by a recently reported case of severe depression who had none of the usual signs and symptoms of Cushing's syndrome other than depression and osteoporosis, but who had 24-hour urinary 11-oxysteroid levels of 11 mg., 16.2 mg. and 18.4 mg. Following a subtotal adrenalectomy the patient's depression was relieved, and his 11-oxysteroid level returned to normal.[40] It is apparent that the development of the classic symptoms of Cushing's syndrome depends not only upon the adrenal steroid level but also upon some unknown metabolic factor or factors.

The present case also raises the question whether emotional factors can lead to the production of Cushing's syndrome. Plotz, et al.,[27] reports that 17 of 97 patients with Cushing's syndrome showed no demonstrable pathology on autopsy other than Crooke's changes in the pituitary and adrenal cortical

hyperplasia, and one case showed only adrenal cortical hyperplasia. Laqueur[41] found Crooke's changes occurred in patients who had received ACTH or cortisone over extended periods, and suggested that these changes were secondary to the prolonged elevation of corticosteroid levels. Thus over 18% of a large series of patients with Cushing's syndrome had no demonstrable pathology other than that associated with a protracted elevation of the corticosteroids. In view of the known relationship between psychobiological stress and adrenocortical functioning it would seem possible that emotional factors are of etiological significance in certain cases of Cushing's syndrome. Such cases would most probably present a clinical picture of adrenal cortical hyperplasia. In such cases a trial period of chlorpromazine administration and psychotherapy would appear to be indicated before the more radical procedures of pituitary irradiation or adrenalectomy are utilized.

The question of etiology also arises when an attempt is made to evaluate the importance of emotional stress in the production of the patient's hyperadrenocorticism, and the effect this elevation of adrenal corticoids in turn had upon the patient's emotional problems. Hypothetically, a circular relationship could be involved whereby anxiety would stimulate an increase in the adrenal steroid level and this in turn would lead to an exacerbation of the patient's emotional problems and anxiety. The degree to which such a relationship was active in the patient is difficult to establish, however, the patient's emotional state varied greatly during August and September while her corticoid level remained remarkably stable. Apparently this reciprocal relationship was not of primary importance in this patient when she was receiving chlorpromazine.

Summary

Extensive psychiatric and physiological data concerning a case of hyperadrenocorticism showing anxiety, depression, polydipsia, and polyuria are presented, and the patient's treatment with chlorpromazine is described.

During the three months prior to hospitalization the patient showed elevations of her 24-hour urinary 17-ketosteroids (mean, 15.5 mg.), 17-hydroxycorticosteroids (mean, 27.3 mg.), and total 24-hour urinary volumes (mean, 6700 ml.). Following hospitalization and the administration of chlorpromazine the patient's average 24-hour urinary 17-ketosteroid excretion was 10.2 mg., her 17-hydroxycorticosteroid excretion averaged 10.2 mg., and her average daily urinary output was 2760 ml. These reductions are attributed to chlorpromazine, and this hypothesis is extensively discussed.

The patient's symptoms of polydipsia and polyuria are examined from the psychodynamic and physiological points of view.

The possible relationships between adrenocortical functioning, mental processes, and mental illness are explored and the literature reviewed. It is hypothesized that psychological factors are of primary importance in the etiology of certain cases of Cushing's syndrome.

A therapeutic trial of chlorpromazine is recommended in cases of adrenal cortical hyperplasia before more radical procedures are utilized.

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The Place of Insulin in Psychiatric Treatment

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In 1927 in Vienna, Sakel introduced into psychiatry the first biological type of treatment. In spite of the onslaught of the pharmaceuticals, electroshock, metrazol shock, and lobotomies, all of which have had their alternating episodes of acceptance and rejection, insulin therapy has had a constant following and, by present statistics, is actually experiencing a resurgence in popularity as the treatment of choice in early mental illness.

Although many large state hospitals have had to eliminate their deep coma units, this has not prevented other institutions, especially private sanitaria and hospitals, from continuing to use insulin therapy in its varied forms. There is some confusion as to exactly what is meant by insulin therapy and by way of brief explanation, it may be broken down into the three types: (1) Insulin Stimulation,[1] (2) Subcoma Insulin Therapy, (3) Coma Insulin Therapy. The last has fallen into disrepute because it is not economically feasible to continue this high type of therapy. Unfortunately, if we try to measure treatment against cost in dollars and cents, we are starting on a road which will eventually suggest that euhtanasia be a cheaper way of taking care of our mental patients.

From Fuller Memorial Sanitarium, So. Attleboro, Mass.

Presented on World Tour of Eastern Psychiatric Research Ass'n. July and August 1960, at Tokyo, Bangkok and New Delhi.

Insulin Stimulation

This therapy has been in use at the Fuller Memorial Sanitarium prior to the advent of electroshock therapy. We use this treatment in about 20 per cent of our 500 annual admissions. It has been used in cases of mild and marked depression, psychoneurosis,

character disorder, schizophrenia, alcohol and drug addiction. We have found that insulin stimulation is part of the physical approach to treatment and fits in smoothly with current pharmaceutical and electroshock therapy. It is not a panacea, or an exclusive treatment, but it is a vitalizing process and is on an acceptable biophysical basis. The nature and action of insulin is not entirely clear. It might, however, be said that hypoglycemia produced by insulin stimulates the body to re-establish homeostasis. Insulin is a biological substance and is acknowledged to produce improvement and recovery in the nerve cells.

Technique of Treatment

A patient is first tried on a sensitivity dose of the drug, and if there are no untoward reactions he is given the starting dose of ten to fifteen units which is thereafter regularly increased. Injections are given early in the morning, usually at 6 A.M. For simple insulin stimulation, a single dose method is employed. Pulse, respiration and blood pressure are taken during the first 15 minutes and checked frequently thereafter. The patient is under constant observation of trained personnel. Insulin patients are treated in a special department.

This type of therapy does not produce coma but a certain degree of relaxation is accomplished. The patient is usually informed as to the type of response expected, namely, sweating, drowsiness, palpitation, difficulty in focusing. Since the patient is alerted to these reactions, he is not alarmed when they appear; in fact, he may be disappointed if the warning does not materialize. On the average, this type of patient is treated for three to six weeks, sometimes longer in cases of severe emotional disturbance. Treatments are given five days of the week. We have, in some instances, continued to treat patients on an out-patient basis if substantial benefits have been shown in the hospital.

We do not feel that insulin coma therapy is an ideal office procedure, but some physicians have successfully continued to treat patients in an office or on an out-patient basis following good progress under hospital conditions. The difficulty of controlling caloric intake and carbohydrate consumption in the out-patient poses a problem.

We have noted over the years that our patients are willing to cooperate with this treatment since they find that it is less drastic than shock therapy, and that they will experience a feeling of well being after the treatment and that they are invariably relaxed by it. Our program calls for a shower and short relaxing massage after the treatment. The patients then have their breakfast generally with ravenous appetite. We have felt that the patient's attitude toward food is a turning point in his illness, and once he begins to experience these changes at an oral level, other physiological changes occur concomitantly. Most treatments are complete before 10:30 a.m., giving an opportunity for individual psychotherapy if necessary. Direct reassurance and supportive psychotherapy can often be given with impressive results during the early phases of treatment.

Remarkable weight gain can be achieved with insulin stimulation treatment. Patients have added 10 to 15 pounds within a month and with this increase in weight, there is emotional improvement. If the treatment program demonstrates a need for electroshock, this is usually given at the end of the treatment period. Many patients do not require intravenous anesthesia because of their semicomatose condition and we have found that electroshock in itself is an excellent method of terminating insulin subcoma. Ordinarily patients are terminated simply by glucose, rarely by gastric lavage, and very infrequently by intravenous glucose. Our termination has been very much facilitated by the use of Glucagon. This is a naturally occurring hormone produced by the Alpha cells of the pancreatic islets. It is capable of creating a rise in blood sugar level even in the presence of a high amount of insulin. It can be administered intravenously or intramuscularly with a large margin of safety and also eliminates the need for carbohydrate which may be undesirable because of its high caloric content.

Insulin stimulation therapy is a treatment which is easily administered and can be well controlled. It has proven useful in combination with electroshock therapy, energizers, and tranquilizers. We generally determine the patient's need for insulin or electroshock therapy upon the findings in the autonomic nervous system reaction. A high adrenalin precipitable anxiety with changes in systolic pressure of major magnitude generally indicates an excellent prognosis for insulin stimulation and subcoma therapy.

Subcoma Therapy

Subcoma therapy implies a deepening of the comatose process as experienced in the stimulation phase, and a larger amount of insulin is generally used. We have adopted the multiple dosage which allows us to produce coma more quickly, and unit for unit, less insulin need be given. We have found that administering in multiple doses, the total amount is smaller than the single dose of older techniques.

The multiple dose method for insulin coma was designed with two objectives in mind; to let the patient have full coma as early in the treatment as possible and to insure lucidity and physical well being in the afternoon so that he may benefit from the complete program of the psychiatric facility. As a general rule, most patients will develop satisfactory coma when given 45 to 60 units of insulin in divided doses, 15 or 20 units every 15 minutes.

The patient is permitted to reach the "safe stage of coma" described by Laquer. This is attained when the patient does not respond to his name or to pain stimuli indicating complete unconsciousness. Symptomatology consists of tonic twitches, facial contractions, extra pyramidal symptoms, and incoordination of the eye axis. We do not permit our patients to remain long even in this safe stage of coma, and treatment is terminated by gastric lavage, intravenous glucose, or electroshock where the program includes this therapy. It has also been found that Glucagon, given intramuscularly, makes the termination of this phase much less complicated and much less risky than the older methods. On awakening with Glucagon, a patient can drink carbohydrate solution without help.

Deep Coma Therapy

We have resorted to this type of therapy only on a few occasions. Deep coma therapy requires skill in the treatment and competent help. It has great value in certain intractable psychiatric conditions. It is important, however, to have trained personnel experienced in this type of therapy. At a recent institute at the Creedmoor State Hospital in New York, a demonstration by H. P. Laquer, M.D., and Harry A. LaBurt, M.D., with their very efficient and well-trained staff demonstrated to members of the symposium sponsored by the Sakel Foundation two groups of insulin patients in deep therapy. The fact that over 35 institutions, using insulin therapy, were represented at this symposium indicates the wide-spread use of insulin therapy. The ever-increasing awareness that psychiatry is dealing with a biologic entity should direct the inquisitive mind and scientific nature to explore further a discipline which will cure mental sickness. Insulin therapy is not only an effective form of treatment, but also gives a lead to the development and testing of a hypothesis linking clinical improvement with physiological change. In addition, it has made a unique contribution as a model of a controlled experimental situation involving acute stress in the human.

The results of insulin therapy are somewhat different from those claimed for the newer drugs. The drugs may facilitate the recovery of the patient to a social level and often permit him to live in the community. However if the dosage is altered or the drug stopped, the patient often regresses. Primarily, therefore, the drug is simply controlling the patient by chemical methods to help him make an adjustment outside of a hospital whereas he required hospitalization before such treatment.

A different situation exists with the technique of insulin therapy. After a certain pe-

riod of satisfactory treatment, the therapy is completely stopped and, we might say, it has had a curative value.

If the trend continues where many thousands of patients are kept on drug therapy alone associated with some psychotherapy, I wonder whether we are doing the right thing by our psychiatric population. I believe that equal if not better results could be procured if insulin therapy were given at the beginning of the patient's treatment. Despite the claims of the newer drugs, it would appear that insulin treatment is the first choice in the early schizophrenic, and it has not been replaced by any other treatment. I believe effort should be made to combine these newer drugs with insulin therapy rather than to substitute the drugs for insulin treatment. I do not think very much has been done in this respect as those firm adherents of insulin therapy, like fanatics in any other good cause, are apt to rely exclusively on one method of treatment and not give the patient the full range of available medication and treatments.

Clinical Changes Produced By Treatment:

In patients who are going to react well to insulin therapy, it is generally found that after the first few comas, wakening from coma leads to an hour or two of considerable improvement. Most prominent is the change in rapport and affective attitude. The amount of insight into the delusions and feelings of unreality acquired after a few comas is often times very impressive. As the treatments continue, the beneficial changes last longer. This is most noticeable in the excited, agitated or panicky type patient who is often much improved in a short time. Generally, within two weeks of treatment there is sufficient progress to justify continuation and, in fact in that time, often a complete remission of the psychoneurotic type of anxiety can be attained.

As with electroshock, it does not appear that there is any magic in numbers. The number of comas is necessarily a matter of debate and clinical trial. Our experience, however, has pointed out that an average of 28 insulin treatments has produced the best results. Improvement, however, is not always obtained before the end of treatment and in many cases recovery is not fully complete until two to four weeks after the course of treatment has been completed.

Electroshock Therapy with Insulin:

Although electroshock therapy itself has proven disappointing in the treatment of schizophrenia, when combined with insulin, it is of great value, especially in the first illness. There is a high percentage of patients who improve with ECT plus insulin but do not respond to insulin alone. With continued treatment the convulsive treatment may no longer be effective, but insulin alone may produce improvement.

It has been observed that many patients who have failed to respond either to ECT or insulin separately cleared up satisfactorily when the two modalities have been combined. The combination often shortens treatment and should always be tried even though insulin or electroshock have failed before. We frequently continue to treat a patient on a "combination treatment" wherein a patient will receive ten electroshock treatments for every two insulin comas. The actual number is determined by clinical response.

We have noticed that the post-shock excitement and often anxiety, which electroconvulsive therapy will produce is entirely eliminated when insulin therapy is used concurrently.

Insulin Therapy with Drugs:

We have often used insulin on patients who have shown an overwhelming response to adrenalin when tested with the ANSR. We combine a biological and pharmacological approach. Patients have received currently with insulin therapy, phenothiazines, particularly in low dosage fluphenazine (Sevinol-Schering). We have not found any contraindications to the dual usage of two agents both designed to allay anxiety. In fact, we find that their effectiveness has increased with concurrent use. We have found that patients who experience under insulin an abreaction accompanied by severe hyper-

kinetic conditions and restlessness with noisy excitement, can be controlled with fluphenazine given parenterally. This produces a deeper and quieter stage of coma and often permits the patient to complete a series of insulin treatments which otherwise may have had to be discontinued for fear of physical harm to the patient.

Most of the current antidepressant agents do not have calming or tranquilizing qualities and very often incite a restless agitation in certain depressed patients. We have found that insulin readily controls these complications and that there have been no contraindications to utilizing monoamine oxidase inhibitors in conjunction with insulin therapy. Where antidepressant therapy by drug alone has been chosen, full dosage of the antidepressant agent can be given safely with insulin therapy, particularly in the sub-coma range of treatment. Phenelzine (Nardil—Warner-Chilcott) 15 mg. q.i.d. has proven an excellent agent in our experience.

The inevitable lag which precedes recovery in patients treated with antidepressant agents is often associated with mounting anxiety. Sub-coma insulin has produced excellent calming qualities during this phase and, due to its beneficial metabolic effect in increasing appetite, composure and general well-being, facilitates complete recovery.

We have found no contraindication to tranquilizers or to antidepressant agents in our insulin coma patients provided they are prescribed in the recommended dosage and are indicated by clinical conditions.

Summary

Results obtained by insulin treatment vary from one individual to another. A rapid gain in weight in a patient suffering from anxiety and hysterical symptoms or from a reactive depression indicates an excellent prognosis. As much as 7 pounds in the first week is not an unusual finding. Poor results will be obtained if the wrong patients are chosen. Endogenous depressives, obsessive compulsive neurosis are generally unrewarding.

Insulin is a companion therapy to electroshock, to energizers, and to tranquilizers. However, the satisfactory selection of patients is vital and indiscriminate use of insulin is to be condemned.

With the selection of the right patients and the correct methods, insulin stands today as one of the major therapies which can be successfully used in a wide range of psychiatric illness. As further studies in metabolism, biochemistry and responses to physical and chemical therapies are carried out, we may hope to have a clearer understanding of these mental illnesses and better differential diagnoses.

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Effect of Drugs on "Poor" Treatment Cases

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Introduction

In many out-patient psychiatric clinics, patients are categorized as "good treatment cases" or "poor treatment cases." Of course, there must be a great deal of variation from clinic to clinic as to what attributes make a patient a "good" or a "poor" treatment case; but generally patients who are poorly motivated, who have little formal education, who are not young and who do not verbalize well, fall into the "poor" treatment group.

The terms used to describe the types of patients selected for different treatments also vary but usually the "good" treatment case is referred for individual psychotherapy. It has been previously pointed out that the more similar the therapist and the patient, the greater the likelihood that individual psychotherapy will be suggested.

Patient Group

There were 10 women and 14 men in the group and their ages ranged from 19 to 57 years.

Apparently "poor" treatment cases are not limited to any particular diagnostic group since there were 16 different types of reactions in the patients seen as shown in Table I.

TABLE I

Diagnosis	*No. of Pts.*
PSYCHONEUROTIC REACTION	
Obsessive Compulsive Reaction	3
Phobic Reaction	3
Depressive Reaction	3
Conversion Reaction	1
Anxiety Reaction	1
Other	1
PERSONALITY TRAIT DISTURBANCE	
Passive Aggressive Personality	2
Compulsive Personality	1
Inadequate Personality	1
SOCIOPATHIC PERSONALITY DISTURBANCE	
Alcohol Addiction	1
Antisocial Reaction	1
INVOLUTIONAL PSYCHOTIC REACTION	1
SCHIZOPHRENIC REACTION	
Paranoid type	1
Simple type	1
PERSONALITY PATTERN DISTURBANCE	
Schizoid Personality	2
Paranoid Personality	1
Total	24

Methods

The patients were seen weekly by the same psychiatrist during the period of study. Each interview lasted 15 to 30 minutes and the approach varied according to the patient's needs and mental state. In an effort to minimize the effects of the interview, no medication was given until the fifth visit. It was felt that by this time the favorable influence of being seen regularly would be apparent and would not be attributed erroneously to the drug.

Two active preparations, chlordiazepoxide (Librium) and ectylurea (Levanil) and a placebo were given orally in identical capsules. Both active drugs and the placebo were given for a period of two months each. In the hope that the patients would experience subjective relief which would increase their motivation to stay in treatment, the active preparations were given first and the placebo later. The interviewer was aware when the medications were changed but the patients were not.

The dosage of chlordiazepoxide (Librium) varied from 20 to 100 mg. daily with an average of 50 mg.; and the dosage of ectylurea (Levanil) varied from 600 to 1200 mg. daily with an average of 900 mg. When the placebo was substituted, the patient received the same number of capsules he had been taking previously of the active compound. On the basis of the patients' statements and

The chlordiazepoxide (Librium) used in this study was furnished by Roche Laboratories and the ectylurea (Levanil) by Upjohn Company.

From the Illinois State Psychiatric Institute, Chicago, Illinois.

their having their prescriptions refilled regularly, all but two of the 17 patients who completed the study apparently took their medicines as directed.

Results

Of the 24 patients 17 completed the seven months' study.

The diagnosis, drug being given, circumstance of withdrawal from the group and the duration of their participation in the study are shown in Table II.

Of the 17 patients who finished the study, only 10 were able to go through the successive changes of medication without need of return to a previously given drug. Seven patients developed an exacerbation of their symptoms following the change from chlordiazepoxide to ectylurea. It was necessary to return these seven to chlordiazepoxide and maintain them on this medication until the end of the study.

The degree of response to treatment was tabulated according to the following grading: No apparent change, improved, and marked improvement. The criteria used for evaluation was: Improved, a reduction of anxiety with a modification of the patients' symptoms and an increased ability to function in their environment. Marked improvement, the patient became more comfortable with a reduction or disappearance of psychotic or psychoneurotic symptoms and showed a marked improvement in ability to function in his environment. These results are shown in Table III.

Patients who had to be returned to chlordiazepoxide are shown in Table IV.

Seven of the 24 patients dropped out of the study during the first eight weeks. Of the 17 patients who finished the study, 16 showed improvement to some degree. However, seven experienced an exacerbation of symptoms during the fourth month of the study while receiving ectylurea and had to be returned to the first active compound given, chlordiazepoxide. It appeared that in these seven the improvement resulted from a specific effect of chlordiazepoxide.

The other 10 patients who were judged improved, maintained this improvement on both active compounds and the placebo. These were considered non-specific effects and unrelated to the compounds being evaluated.

Discussion

Rosenthal and Frank (1958) reported in a study done at the Phipps Psychiatric Clinic that approximately one of every three patients selected for psychotherapy failed to accept it; and three of every four patients who began psychotherapy, terminated with-

TABLE II

DIAGNOSIS	No. Pts.	Drug Being Given at Time of "Drop Out"	Circumstance	Duration of Participation
Schizophrenic Reaction Paranoid Type	1	Chlordiazepoxide	Exacerbation of symptoms. Required hospitalization.	9 weeks (Irregular)
Psychoneurotic Reaction Obsessive Compulsive	1	Chlordiazepoxide	After initial improvement returned to work suffered regressive episode. — Required hospitalization.	10 weeks
Personality Pattern Dist. Schizoid Personality	2	Chlordiazepoxide	Both cases withdrew from the clinical study without notification.	8-10 weeks
Personality Trait Dist. Pass. Agg. Personality	1	Chlordiazepoxide	Began drinking and was arrested for his acting out behavior.	10 weeks
Sociopathic Personality Dist. Addiction Alcohol	1	None	Withdrew without notification.	1 week
Antisocial Reaction	1	None	Withdrew without notification.	2 weeks

Total number of patients who "dropped out"—7

TABLE III

No Apparent Change	Improved		Markedly Improved	
Schizo-Reaction	*Psychoneurotic Reactions*		*Involutional Psychotic R.*	1
Simple Type	1	Phobic	3	*Psychoneurotic Reaction*
		Obsess. Comp.	1	Depressive 1
		Conversion	2	
		Depressive	2	
		Anxiety	1	
		Other	1	
		Person. Trait Disturbance		
		Inadequate Personality	1	
		Passive Per.	1	
		Compulsive Personality	1	
		Paranoid Per.	1	

TABLE IV

Improved

Psychoneurotic Reaction	
Phobic	2
Obsessive Compulsive	2
Other	1
Anxiety	1
Personality Pattern Disturbance	
Paranoid Personality	1

out discussing this step with their therapists. Of the patients who did accept psychotherapy about six out of ten were discharged as unimproved. This report was based on 3413 new patients of whom only 17% were referred for individual therapy. Other clinics report similar experiences.

In view of the relatively poor results reported with insight based psychotherapies in out-patient clinics, the findings in this study would encourage the use of anxiety relieving medications in the "good" as well as the "poor" treatment case. It would appear more desirable to combine insight and drug therapy than to refer patients for either individual psychotherapy or drug therapy only.

The occurrence of 16 types of reactions in 24 patients implies that either very specific diagnostic criteria exist which permit the diagnostician to separate one reaction from another with great accuracy, or that a considerable overlap in symptomatology exists in the various reactions which allows the physician to categorize the patient according to his particular preference. The latter possibility appears more likely. In this group there was no outstanding type of reaction that would indicate a "poor" treatment case.

Conclusions

Chlordiazepoxide (Librium) was found to be more effective than either ectylurea (Levanil) or placebo in the management of out-patients. Disturbing side effects were not seen with either active compound. Of 24 "poor" treatment cases 17 completed a seven month study and seven patients appeared to respond specifically to chlordiazepoxide. The other ten patients who were considered improved responded to both active preparations and the placebo; these effects were not attributed to the compounds being evaluated.

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Frenquel Corrects EEG Changes and Relieves Symptoms in Porphyria

Z. S. SIKES, M.D.

A number of cases of acute intermittent porphyria with electroencephalographic observations have been reported.[1-6] The cases described by Durand et al.,[2] Kiloh and Nevin[3] and Sikes[7] all showed a characteristic slow wave pattern of from 2 to 7 per second; the slow wave pattern appeared to be in direct proportion to the severity of the porphyric crisis; there was resumption of normal alpha rhythm after clinical improvement.

In another report[7] the psychiatric manifestations of porphyria and those in experimental psychoses produced by lysergic acid diethylamide (LSD) and mescaline are compared. Rinkel et al.[8] and Gastaut et al.[9] have described electroencephalographic changes induced by LSD and mescaline. Rinaldi and Himwich[10] show that the changes induced by LSD and mescaline are corrected by Frenquel. The pattern of enduring electrographic alertness (from specific stimulation of the mesodiencephalic activating system) was reversed. They felt that the action of Frenquel is specific since it does not correct or modify the same alerting picture produced by amphetamine or Meratran. Since LSD and mescaline produce overactivity of the mesodiencephalic activating system, the authors suggest that one would expect that Frenquel has a depressing action on that system. However, they report[6] that Frenquel administered alone does not produce such a change. They reason that the effect of the hallucinogenic drugs is a result of their serotonin-facilitating property, and that the correction of these effects by Frenquel is attributable to serotonin inhibition. With this reasoning in mind the author felt that Frenquel should be tried therapeutically in porphyria, and shortly the possibility to do so presented itself.

Peters[5] has reported two patients with intermittent porphyria treated with Frenquel. One patient was under BAL therapy requiring phenobarbital for control of focal seizures. She remained psychotic until the administration of Frenquel 60 mg. orally daily for four days, after which she made a complete recovery. One case with only abdominal colic was not benefited by 200 mg. of Frenquel given intravenously daily.

Case Report: Case #2 described elsewhere[7] during a previous admission was readmitted on September 23, 1957. The present illness began acutely 24 hours earlier with abdominal pain, headache and motor restlessness accompanied by a weak sensation in the lower extremities. The morning of admission he noticed a pinkish color of his urine. By coincidence he had been seen three weeks earlier by the writer and told to come to the hospital in the event of another attack for a trial on Frenquel. Since his previous discharge May 4, 1956 he had had two attacks treated in his local hospital. On admission the urine was positive for porphobilinogen in 1:160 dilution. He was given 100 mg. Frenquel orally four times daily. On the first and second hospital days 200 mg. Frenquel was given intravenously. On September 25, 1957 the oral dose was increased to 200 mg. four times daily. In addition he received Serpasil 0.25 mg. and Banthine 50 mg. four times daily, both given in the same dosage on previous admission without relief. The response to Frenquel was dramatic, with prompt alleviation of abdominal pain and nausea, disappearance of headache and relief of restlessness and apprehension. Upon his return to the hospital from a weekend pass he greeted his physician in the hall with effusive gratitude for relief of his symptoms. The urine was still positive for porphobilinogen in 1:80 dilution. At this time the electroencephalogram showed a sustained alpha rhythm of 10 waves per second. Voltages were moderately high but within normal range. Hyperventilation had no significant influence. It is considered unfortunate that a repeat tracing was not obtained prior to beginning of the drug, but this omission was influenced by the fact that our patient had to be sent 200 miles round trip for EEG. The patient was discharged October 11, 1957 on maintenance dose of Frenquel 100 mg. four times daily. He has been seen several times since discharge. In October and November 1957 porphobilinogen was positive in 1:40 dilution. In February 1958 he was still comfortable, and urine showed only a trace of porphobilinogen. He has remained essentially comfortable and although during the active phase of his attack he was not entirely free of symptoms he was able to work regu-

larly. The only symptom encountered was occasional mild fleeting abdominal pain. There was no recurrence of headache. An incidental finding since discharge has been mild abdominal pain and positive porphobilinogen in the urine of the patient's 10 year old son.

Without the benefit of further and more refined study, any conclusions based on this one case report are purely conjectural. Since some time had elapsed between the idea and the opportunity for the trial, the case was felt worthy of reporting. The electroencephalographic changes seen in intermittent porphyria are evidence of central nervous system involvement. Two possibilities in the production of at least a part of the clinical syndrome are direct interference with neuronal metabolism or a serotonin-enhancing mechanism of porphyrins. The case may add to the evidence that part of the symptoms result from the action of porphyrin on smooth muscle as described by Eliaser and Kondo[11] and Coffman and Kuhl.[1] It is believed that further trial of Frenquel in the symptomatic relief of intermittent porphyria is warranted.

Summary and Conclusions

A single case of intermittent porphyria treated with Frenquel has been described. Electroencephalographic changes seen in porphyria were corrected and symptoms were relieved in this case. Theoretical possibilities as to the mode of action of porphyrins in producing the clinical syndrome of porphyria are discussed.

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The Status and Usefulness of the Psychiatrist

THOMAS R. KEARNEY, M.B.

It is the intention of the writer, who has trained as a psychiatrist in both Europe and the United States, to discuss the relationship of the psychiatrist to other physicians and to the community, and also to scrutinize what may be regarded as the scope of psychiatry, what it does actually perform as opposed to what one would like to think it achieves.

In this country one might begin within the medical school and consider how the psychiatrist is regarded by others with whom he comes in contact. By and large, the American medical student is well trained in psychiatric principles today, in contrast to his senior colleagues. His understanding is bound to be academic rather than practical however, and he often seems to view psychiatry as something vaguely extracurricular. The isolation of psychiatry, which begins in medical school, is emphasized after internship when it becomes more and more cut off from the main stream of medicine.[1] This may be due to the failure of instructors to stress the importance of the psychiatrist being accepted by other doctors. In other countries the necessity for this acceptance receives more support and men are actively encouraged to work in internal medicine or neurology before entering psychiatric training. The Maudsley Hospital, the chief training institute in Great Britain, does not accept candidates with only one year of internship and no background in medicine or science. In America, however, the situation has changed little since 1944 when Gregg[2] said to the American Psychiatric Association, "Most psychiatrists are so ill trained in medicine that they cannot command the respect which would welcome them as collaborators on the wards of a general hospital." Without expressing themselves so strongly both Alvarez,[3] in "The Neuroses," and Palasota,[4] in describing his work in a medium-sized community, bring out the point that a sound knowledge of medicine is essential. It seems that there is a connection between the medical knowledge of the psychiatrist and the way in which other doctors look at him, and that this relationship with his colleagues is reflected in his relations with the community. This has been pointed out by Morris,[5] in the Beattie-Smith lectures at Melbourne University in 1958, where he said, "Until the psychiatrist is better accepted among his medical colleagues . . . it is unlikely that he will receive a sufficient degree of acceptance by the community in general."

There are many ways in which the psychiatrist may hinder this acceptance, the most immediately obvious being by the use of jargon and incomprehensible technical terms. This is frequently referred to in the literature, not only by Gregg, above, but by Appel,[6] Kahana,[7] and L. P. Ferron.[8] This kind of behavior only infuriates other physicians and it will be difficult to gain their respect if there appears to be no community of interest, no common ground on which to meet and no mutual tongue in which thoughts may be exchanged. In the general hospital it seems vital that the consulting psychiatrist know something about the physical problem and the proposed medical or surgical regime. The psychiatrist who does not know that digitalis sometimes makes patients vomit is a distressing sight. Indeed, in mental hospital practice it is only reasonable that the psychiatrist be able to manage ordinary medical conditions as well as the average general practitioner. He certainly has as much time as the general practitioner to keep abreast of the rudiments of medical advances, and he should not have to call an internist to treat a patient with an uncomplicated duodenal ulcer or lobar pneumonia. In doing so, he fosters the concept of isolation to which the writer has referred above—the "Ivory Tower" philosophy. Furthermore, the reluctance of some therapists to take note of the bodily symp-

toms of their patients, or to examine them even at the beginning of treatment, is hardly desirable. If the physician refuses to behave like a doctor there can be no reasonable objection to lay therapists entering the field.

Almost all physicians give some free time and do some free work. Few psychiatrists in private practice do so, however, and fewer still extend professional courtesy to doctors, nurses or students. This is something which can be strongly resented and is another wedge driving apart what should be twin disciplines. Wide differences in attitude, particularly about treatment methods, also make psychiatry unique among the medical specialties, and these cleavages of opinion—frequently bitter—and differences in basic fundamental stands do not go unnoticed by our colleagues or by the public.

The public's concept of the specialty stresses its ubiquity in the sense of how widely appropriate it is to apply its doctrines in this or that field; as a consequence, the view is held that an increase in mental health facilities, and in the number of psychiatrists, social workers and clinics will help in the attenuation of mental and emotional illness. Yet, in practice, the opposite is true and the more widely spread the work of the specialty becomes, the more people, in accordance with Parkinson's Law, do we find to call sick.

From time to time psychiatrists are asked to do things which are outside their competence. For example, a colleague may have a dying patient and ask the psychiatrist to break the news to him, thereby evading his own responsibility—and in a rather subtle way rejecting the psychiatrist. It is not uncommon for patients to present themselves because they are unhappy and seek a sympathetic friend. There are, however, many people in the world who are unhappy and many sources of sadness which one can do little to remedy. Unhappiness though an affliction is not a disease and it may take a great deal of intellectual honesty to decide whether one is practising psychiatry or indulging the Pollyanna within one's bosom.[9] Since this country is not going to have enough psychiatrists in the foreseeable future a good relationship with general practitioners and others is extremely important so that they may be encouraged to give emotional support to people who are mildly or moderately ill and refer only the more difficult or urgent cases to the specialist.

It is necessary to have a sense of perspective about one's achievements. In recent years Bartemeier[10] has shown that patients in hospitals with a minimum of professional staff show improvements which are not to be explained on the basis of the treatment they have received. In terms of length of stay and rates of discharge, some less well-endowed hospitals compare favorably with other institutions having more aggressive treatment programs and more trained people to carry them out. It is known that patients with illnesses of acute onset often do well and that those diseases of insidious onset with bad family history carry a poor prognosis regardless of the efforts of the physician. The same question applies in psychiatry as in any other branch of medicine—how much influence does the treatment have on the outcome of the illness? Sloane's work[11] suggests that there are a number of depressed patients who improve without shock or specific drug therapy and that their improvement is related to being in a therapeutic milieu, removed from anxiety-producing factors. To carry the point further, Karagulla,[12] working under Sir David Henderson in Edinburgh, found among 923 patients only minor differences in recovery and relapse rate between those treated with ECT and those treated conservatively. There was no proof that ECT shortened hospital stay appreciably although it seemed to make the illness more bearable.

Reflections like these pose the question of whether we are prone to attribute to our intervention things which would have happened anyway in the course of time. If one reads the recent deluge of papers on antidepressive drugs one sees that some psychiatrists tend to be very sanguine in their conclusions. Many of these reports concern ambulant patients who may, for all one

knows, have given their pills to monkeys in the zoo. The studies are often uncontrolled, and without validity as indices of the response of a specific disease to a specific form of treatment. Psychiatrists are contributing, wittingly or unwittingly, to a climate of opinion which favors magical and omnipotent forces, as therapeutic solutions to the problems of mental and emotional illness of our time.

And yet, psychiatry has a great deal to give to medicine even if there is much to be overcome first. Relentless re-examination of oneself and one's work is called for. Only by careful reappraisal of the training and work of people in this and other countries (because there are other approaches than ours and we may have something to learn from them) can the psychiatric specialty begin to achieve its full potential. There are many who feel strongly that more medical work or general practice should be included in the training of the psychiatrist, that he should have competence in handling ordinary medical problems and that everything possible should be done to emphasize the unity of psychiatry with medicine. Under present circumstances the trend is toward divorce. The American Board of Psychiatry and Neurology requires three years of psychiatric residency and two years of practice before admitting candidates to examination. It is the opinion of this writer that if at least one of these five years were in internal medicine, pediatrics or general practice, some improvement in the present situation might be achieved. In the words of Nadeau,[13] "Le psychiatre et le médecin doivent marcher de pair, la main dans la main, afin d'en arriver a créer une médicine plus compréhensive, plus féconde, parceque plus pleinement humaine." If the present trend towards the separation of psychiatry from medicine continues, if it becomes instead of a branch, a way of life, if it acquires more and more the trappings and language of an esoteric religion, then today's Ivory Tower may yet become the whited sepulcher of tomorrow.

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THE UNIVERSITY OF MICHIGAN MEDICAL CENTER

Postgraduate Course in Clinical Neurology

UNIVERSITY HOSPITAL, ANN ARBOR, MICHIGAN

MARCH 20 AND 21, 1962

The postgraduate course in Clinical Neurology, under the direction of Dr. Russell N. DeJong, Chairman of the Neurology Department, will be devoted almost exclusively to a survey and appraisal of current aspects of treatment—treatment not only of those neurologic conditions most frequently encountered by the practicing physician, but also of those complications of systemic disease that affect the nervous system. Although differential diagnosis and special diagnostic procedures will obviously be mentioned and discussed, stress will at all times be placed upon therapy.

Program and application may be obtained from John M. Sheldon, M.D., Director, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan.

Clinical Neuropathological Conference

Edited by Stanley M. Aronson, M.D., and Haruo Okazaki, M.D.

Presentation

A 50-year-old white male was admitted to the hospital because of drowsiness and confusion of five days' duration.

History obtained from patient's wife indicated that except for recent weight loss (15 lbs. in 3 months) the patient had been in good health until five days prior to admission, when she noticed that he was very sleepy. He went to bed several times during the day. While awake, however, he seemed lucid, until the day prior to admission, when he became confused. That same evening he had his first generalized seizure, lasting two minutes, at the termination of which the patient showed severe confusion. On the day of admission he was very drowsy and disoriented.

There was no serious illness in the past. The only previous hospitalization was caused by fracture of the right wrist and right hip following a fall five months prior to present admission. There was no associated head trauma or loss of consciousness.

The patient lived with his wife and was employed as a plumber's helper until 1958. Since then he has been holding odd jobs. He drank alcoholic beverages for many years, mainly beer, but did not get drunk. He ate well and smoked heavily.

Admission Physical Examination:

Revealed a thin, middle aged male, who at times would answer questions quickly (though incorrectly) and at other times became suddenly drowsy. Blood pressure, 128/80; pulse, 84/min. and regular; respirations, 15/min.; temperature, 100°. No abnormalities were found on examination of chest and abdomen.

The patient was seen in neurosurgical consultation on the day following admission. There was no evidence of head trauma noted but there were multiple minor abrasions of the extremities. The patient was mildly drowsy, confused and disoriented but cooperative. The pupils were equal in size, reacting well to light. There was early, bilateral papilledema. Nystagmoid movements of both eyes were noted (horizontal and vertical) as well as limitation of extraocular muscle movement in all directions. A minimal, left central facial weakness was described. The gag reflexes were depressed bilaterally. There was no evidence of paresis of the extremities. Coordination (finger-to-nose and heel-to-knee tests) was slightly impaired, bilaterally. Tendon reflexes were brisk and symmetrical; the superficial reflexes were absent. The Babinski toe sign was bilaterally positive.

On the same day, the patient had a generalized seizure and was placed on anticonvulsive therapy. A lumber puncture was performed. Opening pressure was 105 mm. of water. The withdrawn fluid was clear and colorless. Pandy test was negative. Microscopy showed one white blood cell and two red blood cells. On the third hospital day the patient showed a deepening lethargy. He responded to verbal stimulation but his answers were completely irrelevant. Temperature was 101.4°. On the fourth hospital day he responded to verbal stimulation only by looking at the examiner. He did not speak but was still able to follow simple commands. On the fifth day, he was more lethargic, and appeared "aphasic"; he moved all extremities well. Nystagmus and spontaneous nystagmoid movements of both eyes were noted. Bilateral Babinski toe signs were present. Bilateral carotid arteriograms were performed and interpreted as showing no abnormalities. An ophthalmology consultation described the optic discs as blurred with markedly narrowed vessels. There was no evidence of papilledema. A second lumbar puncture was performed. Opening pressure was 60 mm. of water. Pandy test negative; protein, 9 mg.%; glucose, 65 mg.%; chlorides, 99 mg.%. No cells seen.

Additional Laboratory Data:

Hemoglobin, 15.5 gm. %; WBC, 11,400; differential count, polymorphonuclear leukocytes, 87%; immature forms, 1%; lymphocytes, 10%; monocytes, 2%; urinalysis was negative; blood serology, negative; BUN, 10-13 mg. %; fasting blood glucose, 60-79 mg. %.

On the seventh hospital day, the patient became stuporous, responding only to painful stimulation. He was transferred to the Neurosurgical Service where surgery was performed the following day.

Discussion of Clinical Aspects

Dr. Harry A. Kaplan: This case of a 50-year-old white male with drowsiness and confusion of five days' duration represents an instance of some rapidly developing neurologic disorder. One would immediately think of the possibility of some vascular disease, such as the occlusion of an extracranial cerebral arterial channel; an intracranial blood clot, such as a subdural hemorrhage; encephalitis or meningitis. Metastatic neoplasm to the brain or a brain abscess might similarly develop in a rapid fashion, as determined clinically.

From State University of New York, Downstate Medical Center and Kings County Hospital Center, Brooklyn, N. Y.

The patient's wife states that he lost 15 pounds in the three months before admission. The existence of a carcinoma with cerebral metastasis as a basis for this patients illness must be considered. However, a history limited to five days is too rapid and suggests something other than a disturbance based upon metastases. The wife further states that there were lucid periods and some convulsions in the five days before admission. Certainly, a subdural hematoma looms as a very likely possibility. All the signs so far given can be cardinal manifestations of a subdural accumulation of blood. We are also told that there was a history of injury about five months before hospitalization. A subdural hematoma present for five months, however, would not be likely to produce the rapid onset of cerebral disturbance seen in this case. The history, as presently indicated, is more often associated with a subdural hematoma that has been present, perhaps, for several weeks or months. In fact, some subdural collections spontaneously resorb within a five-month period of time. The history of alcoholism would favor the possibility of subdural collection of blood since it is well known that alcoholics, perhaps because of a greater tendency towards trauma, sustain subdural hematoma more readily than non-alcoholics. Some other form of alcoholic encephalopathy is also a possibility.

Further history from the wife indicates that the patient was employed as a plumber's helper and also did odd jobs. It would seem that the patient was of low intellectual capacity. The possibility of some diffuse degenerative brain disease developing over many years must also be considered.

The admission physical examination took note of some alteration in the patient's state of alertness during questioning. Also, multiple minor abrasions were noted on the extremities. These signs, together with the history as given, further suggests the possibility of a subdural hematoma. Drowsiness in people harboring such hemorrhages is usually the result of swelling beneath the collection of blood with secondary compression of the upper brain stem structures. One might anticipate a difference in pupil diameter, although this is not absolutely necessary. The pupils in the patient were equal and reacted well to light.

Until now, a subdural collection seems most likely. However, the next part of the neurologic examination causes one to develop further thoughts about this problem. Nystagmus and limitation of extra-ocular movement are described, changes which practically speaking are never found with mere compression of brain stem structures. This is more commonly an indication of an intrinsic lesion within the brain stem. If there were sufficient brain stem compression to produce bilateral extra-ocular muscle paralysis in all directions, the patient would most certainly be in advanced stupor.

Further examination also indicates a left central facial weakness which might also be the result of a brain stem compression. Yet, the presence of depression of the gag reflex, if pathological, would again suggest brain stem disturbance more extensive than that associated with mere compression in the midbrain area. The absence of any paresis of the extremities and the presence of a deficit in coordination favors an intrinsic disturbance rather than a compressive lesion. It is proper, of course, to consider the outside possibility of a chronic leptomeningitis involving the ventral aspects of the brain which can cause disturbance of blood flow and secondary parenchymatous damage. Lumbar puncture, however, showed clear spinal fluid. I would therefore be hesitant to consider severe meningitis with such spinal fluid findings and the absence of further positive clinical signs.

On the fourth hospital day, the patient was mute and responded to verbal stimulation only by looking at the examiner and following simple commands. This type of clinical state has been noticed with thalamic lesions. The bilaterality of signs, together with the absence of any disturbance in the movement of the extremities, leads one away from the thought of any extensive extra-cranial cerebral arterial occlusion. Furthermore, the carotid angiograms showed no abnormalities. This also would indicate the improbability of a subdural collection of blood. We have seen occasional subdural collections in the occipital regions or beneath the temporal lobe which may not show up with a carotid angiogram; subdural collections in these localities are rare. The physical examination also revealed the absence of papilledema.

I believe that the findings, in summary, are indicative of a lesion or lesions within the midbrain and pons, of a nature producing relatively rapid emergence of symptoms. There are many inconsistencies but the remote possibility of a cerebellar hemorrhage or infratentorial cyst within the midline has to be considered. A subdural hematoma in an unorthodox position should also be entertained, but the most likely patho-

logic entities to account for the clinical state as given to us would be an inflammatory encephalitis, possibly of viral origin and predominantly involving the upper brain stem or a metabolic disturbance in the brain stem, such a Wernicke's encephalopathy.

Discussion of Pathological Aspects

Dr. Haruo Okazaki: The operative procedure described in the last paragraph of the clinical protocol consisted of an exploratory craniotomy involving the right temporo-parietal region. Some tissues were submitted for histologic examination but showed no neoplasm or other pathologic change. No abnormalities were noted grossly during the course of the surgical exploration. The patient did poorly postoperatively, developing respiratory distress which required intermittent suction and finally tracheostomy. Generalized seizures and irregular fever were noted a few days later. Coffee-ground material was suctioned from the stomach two days prior to death. The patient died nine days after craniotomy.

At autopsy, the patient was found to have a fatty liver of moderate degree, weighing 1,600 grams. There were small, acute ulcerations of the gastric mucosa and coffee-ground material filling the stomach. Areas of pneumonitis and tracheo-bronchial aspiration of gastric content were also noted.

A surgical defect, measuring 6 by 4 cm., was noted in the right temporo-parietal region. This defect was approximately 3 cm. in depth. No other gross lesions were found in the brain or in the spinal cord, externally. Some granularity was seen in some portions of the bilateral mammillary bodies and along the walls of the third ventricle, i.e., hypothalamus.

Histologically, striking changes are found in these areas. A diffuse, spongy rarefaction of the tissue in the mammillary bodies and paraventricular hypothalamic region is evident, with hypertrophy and proliferation of small blood vessels, particularly capillaries (Fig. 1). This vascular proliferation is more dramatically demonstrated by means of a reticulin stain (Fig. 2). Occasionally, extensive hyperplasia of the mural cells of these blood vessels is observed. The neurons, particularly in the mammillary bodies are in a relative state of preservation amid the regions of rarefaction and other degenerative changes. In some other places, such as the hypothalamus, the neuronal loss is apparent. Many of the remaining neurons show advanced stages of damage. Moderate astrocytic proliferation accompanies these alterations.

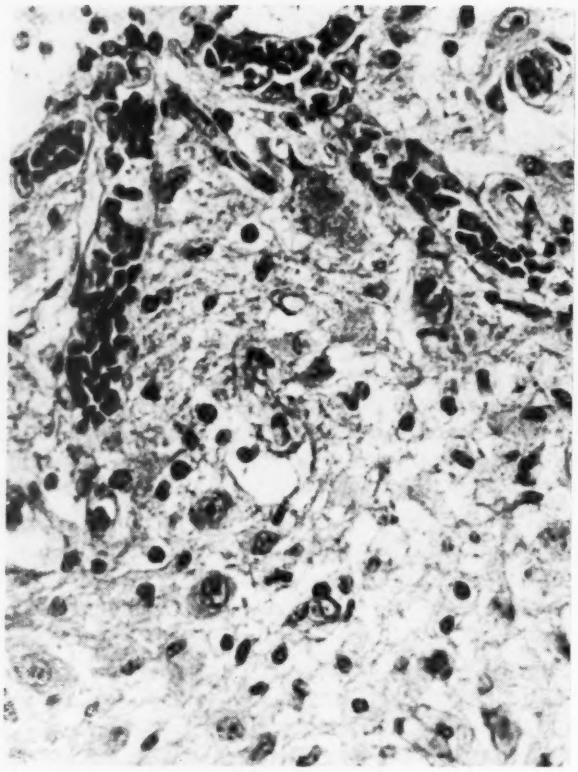

Fig. 1a: Photomicrograph of the mammillary body from the present case (H&E Stain).

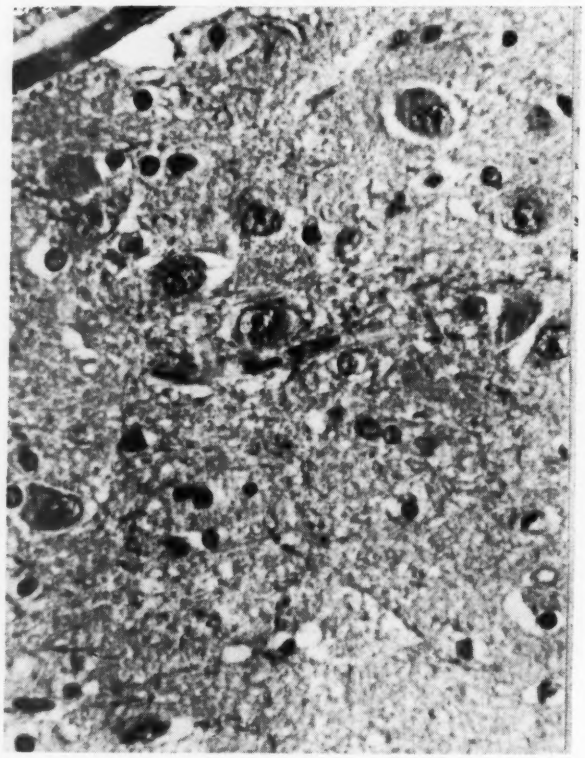

Fig. 1b: Photomicrograph of a normal mammillary body for comparison (H&E Stain).

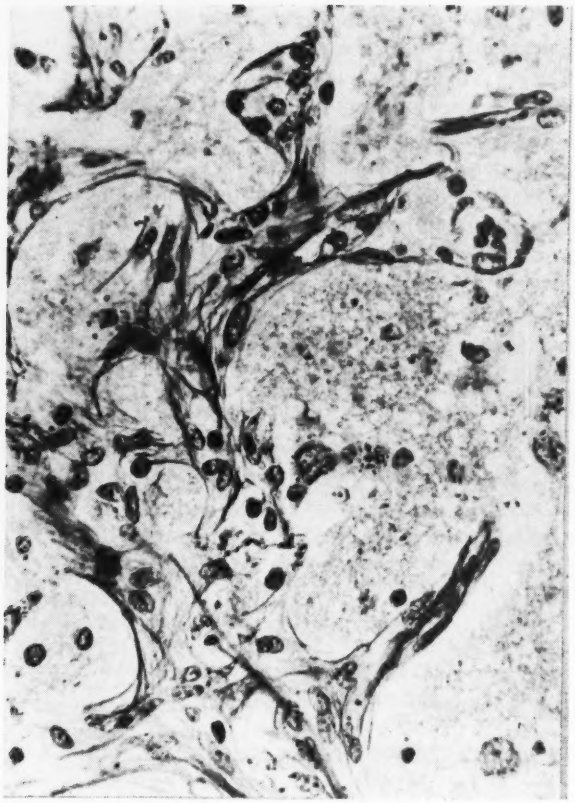

Fig. 2: Photomicrograph of the mammillary body from the present case (Laidlaw reticulin stain).

These changes were first described in 1881 by the German neuropsychiatrist, Karl Wernicke, and commonly known as Wernicke's encephalopathy. The anatomic changes to be anticipated in such cases are listed in the accompanying Table I. Foci of petechial hemorrhage were not noted in today's case but the absence of this hemorrhagic feature is not uncommon. Many of Wernicke's original cases did feature this hemorrhagic diathesis and hence the original title of the disturbance polioencephalitis hemorhagica superior acuta. Of course the term, *superior,* does not cover the involvement of the floor of the fourth ventricle of the lower brain stem, a change which is frequently present in this nutritional encephalopathy.

The topographic distribution of the characteristic lesions in Wernicke's encephalopathy is illustrated in this list (Table II). This case adheres closely to this pattern.

It is with a knowledge of these pathologic changes that the clinical manifestations of this form of encephalopathy are better appreciated and understood.

The *ocular pareses* are primarily due to involvement of the periaqueductal grey matter including the third, fourth and sixth cranial nerve nuclei. These ocular signs are known to respond to thiamin therapy rather promptly (in the early stages of the disease) pointing to the reversible nature of the initial pathologic process.

Nystagmus is generally agreed by most observers to be the earliest and most common finding in this disorder and its presence in a patient with mental confusion should immediately arouse a suspicion of Wernicke's encephalopathy.

Mental changes are more difficult to ascribe to any specific anatomic lesion. It is generally accepted that changes in the cerebral cortex are either absent or too slight and nonspecific in Wernicke's disease and cannot be held responsible for the accompanying mental changes. These mental changes may be characterized as "mental deceleration or disinterest." The patients are usually alert but their spontaneous speech is minimal. They show an inability to sustain attention long enough to carry on conversation and they often mimic aphasia to an inexperienced observer. Answers which they may render to persistent questioning are often perfunctory and irrational. The patients are usually out of contact and show a loss of interest in surrounding events; this is in contrast to the usual hyperactive, apprehensive and hallucinating patient in delirium tremens. About 20% of cases of Wernicke's encephalopathy, however, are ushered in by symptoms of delirium tremens. Nev-

TABLE I

Histopathological Features of Wernicke's Encephalopathy

TISSUE NECROSIS:	spongy rarefaction; microglial proliferation and mild inflammatory cell reaction.
CAPILLARIES:	proliferation of vessels and hyperplasia of mural cells.
ASTROCYTES:	degenerative changes; hypertrophy and proliferation.
NEURONS:	relatively spared; irregular ischemic degeneration.

TABLE II

Common Sites of Lesions in Wernicke's Encephalopathy

Mamillary bodies
Paraventricular nuclei (hypothalamic)
Periaqueductal grey matter
Corpora quadrigemina
Thalamus (dorsomedial nuclei)
Pontine tegmentum
Medullary tegmentum

ertheless, these two conditions are clearly distinct clinical and pathological entities. Parenthetically, no definite structural changes are described in delirium tremens.

Disorientation and impaired memory for recent events are also present but difficult to uncover at the beginnings of the disease; they become obvious over the course of several days as the other neurologic deficits may subside. It should be noted that the mental changes of Wernicke's disease are the most refractile to thiamin therapy.

Ataxia which is primarily shown as a disturbance of stance and gait in this disorder is usually ascribed to the involvement of the vestibular nuclei and their connections.

Autonomic disturbances are manifest as nausea, vomiting, shock or other cardiovascular and respiratory abnormalities and are most likely due to the involvement of the hypothalamic and medullary vegetative centers.

Many patients who recover, either spontaneously or after therapy, are left with varying degrees and combinations of memory impairment, disorientation and confabulatory tendencies, a syndrome first described by the Russian psychiatrist S. S. Korsakoff, in 1887.

Studies on patients with Korsakoff's psychosis (usually chronic inmates of mental hospitals), have shown that most of them present classical or fragmentary aspects of Wernicke's syndrome in their past history. The pathologic changes present can be construed as representing a healed stage of Wernicke's encephalopathy. Thus, it is possible to consider these two syndromes as one and the same disorder viewed at different phases of its natural history. Of course this is not to deny the possibility that many other conditions such as cerebral trauma, unassociated with the lesions described, can be followed by Korsakoff's psychosis. In intracranial neoplasms a relatively selective deficit in recent memory is most likely to occur when there is involvement of the mammillary region. Resection of the medial portions of the temporal lobe, to which the mammillary bodies are associated via the fornices, sometimes results in a similar memory defect. Strangely, however, section of the fornices does not produce such a deficit.

Fatal outcome, one of the cardinal criteria in Wernicke's original description, is no longer considered a necessary part of the syndrome. It is reported in about 14% of some clinical series.

Data on our 35 autopsied cases of Wernicke-Korsakoff syndrome from the files of Kings County Hospital Center are noted in Table III; 89% of the patients were known alcoholics and the rest were probably alcoholics. Interestingly, a clinically determined poor nutritional state was noted only in one third of the cases. This appears to indicate that vitamin deficiency, thiamin in particular (which is considered to be more or less a specific causative factor in Wernicke-Korsakoff disease), is not necessarily associated with an overt state of malnutrition. Pathologically, however, a fatty liver or portal cirrhosis was found in three fourths of our cases.

TABLE III

Wernicke-Korsakoff Encephalopathy

Review of 35 Autopsied Cases

1. Sex:
   Male — 26; Female — 9.
2. Age:
   Average — 51.7 ± 3.9 years.
   Range — 27-54 years.
3. History of Alcoholism:
   Definite — 89%
   Possible — 11%
4. Nutritional State (clinical criteria):
   Adequate — 71%
   Poor — 29%
5. Nutritional Liver Disease (pathologic criteria):
   Fatty liver — 26%
   Portal cirrhosis — 56%
   No hepatic change — 18%

In order to avoid a wrong impression that one might gather from the data collected at this hospital, I would add that many other conditions including gastrointestinal neoplasms, hyperemesis gravidarum, febrile diseases and other miscellaneous debilitating states have also been reported to be associated with this syndrome. As a matter of fact, the original description by Wernicke in 1881 includes a young female suffering from persistent vomiting after the ingestion of sulfuric acid following a suicide attempt. Korsakoff's various papers on the subject also include a variety of underlying conditions.

While the etiologic factor in Wernicke's encephalopathy has been extensively elucidated, there are some crucial points in the pathogenesis yet to be clarified. These include the problem as to what constitutes the primary structure affected in this condition. Another one of the problems is why certain specific areas, as mentioned before, are selectively involved to the apparent exclusion of other intracranial zones.

DISEASES OF THE NERVOUS SYSTEM
INDEX 1961 — VOLUME XXII

ADOLESCENTS IN DISTRESS ---- October 555
Walter Freeman

AGE DISTRIBUTION OF A SCHIZOPHRENIC POPULATION ---- November 616
G. Donald Niswander and George M. Haslerud

ALCOHOLIC PATIENTS—TREATMENT WITH TRIIODOTHYRONINE ---- April 227
James H. Satterfield and Samuel B. Guze

ALCOHOLIC PERSONALITY—PASSIVE AGGRESSIVE ---- January 49
Edward Podolsky

AMBULATORY PSYCHOTHERAPY FOR THE SCHIZOPHRENIC WITH AID OF DRUGS ---- January 45
F. Kant and H. B. Abele

AMITRIPTYLINE IN ANERGIC STATES ---- Supp. May 27
Paul E. Feldman

AMITRIPTYLINE IN TREATMENT OF DEPRESSIVE STATES ---- June 334
Maurice Vaisberg and John C. Saunders

AMITRIPTYLINE: TREATMENT IN DEPRESSIVE STATES ---- Supp. May 55
Douglas Bennett

AMYOTROPHIC LATERAL SCLEROSIS SYNDROME ---- June 305
Desmond S. O'Doherty

ANOREXIA NERVOSA: TREATMENT WITH HYPNOSIS AND ECT ---- November 627
Harry K. Davis

ANTIDEPRESSANT AGENTS (MULTIPLE) IN DEPRESSED PATIENTS ---- October 568
Edwin Dunlop

ANTIDEPRESSANT AGENTS—PHARMACOLOGY ---- Supp. May 7
Vernon G. Vernier

ANTIDEPRESSANTS: A CRITIQUE ---- Supp. May 32
Frank J. Ayd, Jr.

ANTIDEPRESSANTS—COMPARATIVE TRIAL ---- Supp. April 90
George G. Haydu, Walter Brinitzer, John N. McKnight and John R. Whittier

ANTIDEPRESSANT DRUGS—EFFECT ON TESTS OF MOOD AND PERCEPTION ---- Supp. May 24
Adrian M. Ostfeld

ANTIDEPRESSIVE DRUGS IN THE TREATMENT OF DEPRESSION ---- August 449
Pedro Polonio

ANTIDEPRESSIVES: THE PITH OF AFFECTIVE THERAPY ---- Supp. May 37
John C. Saunders

ANXIETY: RELATIONSHIP BETWEEN METHODS OF EVALUATION ---- October 565
Ali A. Kawi

"APPROVAL-HUNGRY" NEUROTIC—A SPECIFIC TYPE ---- August 441
Edmund Bergler

BIOCHEMICAL THEORY OF MENTAL ILLNESS ---- February 101
Jack Behrman

BUTYROPHENONE DERIVATIVES STUDIED WITH CONDITIONED REFLEX ---- November 623
G. F. Golwurm and F. Vanni

CARPHENAZINE (PROKETAZINE) SYMPOSIUM

CHEMISTRY OF CARPHENAZINE ---- Supp. February 5
Peter B. Russell

PHARMACOLOGY AND TOXICITY OF CARPHENAZINE ---- Supp. February 7
Richard Tislow

EEG EFFECTS OF CARPHENAZINE ---- Supp. February 14
Michael J. Hosko, Jr.

BEHAVIORAL PROCEDURES USED IN EVALUATION ---- Supp. February 19
Irving Geller

INHIBITORY EFFECTS OF PHENOTHIAZINES ON BRAIN SELF-STIMULATION ---- Supp. February 23
Larry Stein

PHYSIOLOGICAL REACTIVITY OF CARPHENAZINE ---- Supp. February 28
Anthony Sainz

IDENTIFICATION, DESCRIPTION AND SELECTION OF THE SCHIZOPHRENIC ---- Supp. February 30
Nolan D. C. Lewis

CARPHENAZINE IN THE TREATMENT OF SCHIZOPHRENIA ---- Supp. February 37
Jane E. Oltman and Samuel Friedman

CARPHENAZINE IN SEVERELY ILL PSYCHIATRIC OUT-PATIENTS ---- Supp. February 42
Sidney Merlis

TRIFLUOPERAZINE AND CARPHENAZINE IN CHRONICALLY ILL SCHIZOPHRENICS ---- Supp. February 46
J. Cacioppo, H. Babikian and Sidney Merlis

CHRONIC SCHIZOPHRENIA TREATED WITH CARPHENAZINE ---- Supp. February 51
Douglas Goldman

CARPHENAZINE THERAPY IN HOSPITALIZED PATIENTS ---- Supp. February 58
Nauttam J. Kothari, In Ho Park, Nathan S. Kline and John C. Saunders

CLINICAL EVALUATION OF CARPHENAZINE ---- Supp. February 60
D. W. McCREIGHT

FACTORS THAT DETERMINE DRUG-INDUCED AKATHISIA ---- Supp. February 69
Daniel X. Freedman and Jacob deJong

COMPARISON OF CARPHENAZINE AND FLUPHENAZINE IN CHRONIC SCHIZOPHRENICS Supp. February 77
Anthony Sainz

SUMMARY OF PHARMACOLOGICAL AND CLINICAL STUDIES OF CARPHENAZINE ---- Supp. February 80
Joseph M. Tobin

CHEMOTHERAPEUTIC TRIALS IN PSYCHOSIS. IV ..... January 23
Wm. J. Turner, Victoria Hania, Seymour Halpern and Sidney Merlis
CHILD ANALYSIS—COMMENTS ON THE PRESENT STATUS ..... July 404
Herbert Freed

CHLORDIAZEPOXIDE (LIBRIUM) SYMPOSIUM

PHARMACOLOGY OF CHLORDIAZEPOXIDE ..... Supp. July 7
Lowell O. Randall
ELECTROPHYSIOLOGICAL CORRELATES OF CHLORDIAZEPOXIDE ..... Supp. July 16
William G. Clark
CHLORDIAZEPOXIDE AS AN ANTI-CONVULSANT ..... Supp. July 17
Nicholas Bercel
"STARTLE" EPILEPSY TREATED WITH CHLORDIAZEPOXIDE ..... Supp. July 20
Norman H. Cohen, Maire McAuliffe and Robert B. Aird
CHLORDIAZEPOXIDE IN CLINICAL PRACTICE ..... Supp. July 28
Sidney Cohen
LIBRIUM ON ATHETOID PARAPLEGICS (FILM) ..... Supp. July 39
Robert F. Livingston
CHLORDIAZEPOXIDE IN TREATMENT OF ALCOHOLICS ..... Supp. July 44
Horace B. Mooney, Keith S. Ditman and Sidney Cohen
METHODOLOGY AND PSYCHOLOGICAL TESTS IN EVALUATION ..... Supp. July 52
Harry Grayson
EFFECTS OF LIBRIUM IN PSYCHIATRIC DISORDERS ..... Supp. July 60
Max Hayman

CHLORHEXADOL, A NEW HYPNOTIC ..... October 562
Oscar Rozett
CHLORPROMAZINE IN DIFFICULT PEDIATRIC DENTAL PATIENTS ..... May 282
Saul I. Harrison and Raymond H. Sawusch
CHLORPROTHIXENE (TARACTAN) IN PRIVATE PRACTICE ..... March 154
Harry F. Darling
CHLORPROTHIXENE ON SCHIZOPHRENIC PATIENTS ..... November 636
Albert A. Kurland and Esber Yazicioglu
CLINICAL NEUROPATHIC CONFERENCE ..... December 700
Stanley M. Aronson and Haruo Okazaki (Editors)
COLOR IN DREAMS—SIGNIFICANCE ..... May 278
Nathan Roth
COMBINED DRUG THERAPY OF CHRONIC SCHIZOPHRENICS ..... July 370
Eugene M. Caffey, Jr. and C. James Klett
COMMUNICATION FOR THE PSYCHIATRIST ..... February 109
John D. Moriarty
CONDITIONAL REFLEX TECHNIQUE: EVALUATION OF ANTIDEPRESSANT ..... Supp. May 14
Leo Alexander
CORPUS CALLOSUM ..... August 428
J. U. Toglia
DE-INSTITUTIONALIZATION OF PATIENTS ..... January 26
M. G. Evangelakis
DEOXYRIBONUCLEIC ACIDS—BIOLOGICAL ACTIVITY ..... Supp. April 9
Aaron Bendich
DEPRESSION—MASKED ..... Supp. May 41
Wilfred Dorfman
DEPRESSION—MENTAL ..... Supp. May 5
William L. Holt, Jr.
DEPRESSION: TREATMENT IN PRIVATE PRACTICE ..... Supp. May 46
Edwin Dunlop
DIMENSIONS OF CHANGE IN PSYCHIATRIC SYMPTOMATOLOGY ..... October 576
Donald R. Gorham and John E. Overall
DIRECTIVE TECHNIQUES AND PSYCHOTHERAPY WITH CHILDREN ..... September 494
William H. Tragle and James N. Sussex
DITRAN—EFFECT ON CHRONIC, REGRESSED MENTAL PATIENTS ..... May 268
William N. Karn, Jr., Beverley T. Mead and J. J. Fishman
DURATION OF IMPAIRED CONSCIOUSNESS AS INDEX OF SEVERITY IN HEAD INJURIES February 69
Aaron Smith
ELAVIL—ANTIDEPRESSANT QUALITIES ..... Supp. April 107
Edwin Dunlop
ELAVIL—A NEW PARENTERAL ANTIDEPRESSANT ..... March 145
Wilfred Dorfman
ELECTRIC AND CHEMICAL CONVULSIVE THERAPY IN PSYCHIATRY ..... February 91
David Impastato
ELECTRIC SHOCK THERAPY—A MISNOMER ..... January 18
Ernest C. Miller and Martha Kelly
ELECTROSTIMULATION ON BRAIN 5-HYDROXYTRYPTAMINE CONCENTRATION ..... Supp. April 93
Carl Breitner, Albert Picchioni, Lincoln Chin and Lloyd E. Burton
ELECTROSTIMULATION THERAPY AND DRUGS ..... Supp. May 50
Paul H. Wilcox
EEG CHANGES ASSOCIATED WITH CHRONIC ALCOHOLISM ..... May 284
Mark Dyken, Phyllis Grant and Philip White
ETRYPTAMINE, A NEW AND SAFER ANTIDEPRESSANT CHEMICAL ..... August 452
Theodore R. Robie

EVOLUTION OF THE CARE OF THE MENTALLY ILL — April 208
Percy G. Hamlin
FEASIBILITY OF "BROWSING" DOUBLE BLIND STUDIES — April 223
A. K. Shapiro, K. T. Dussik, J. C. Tolentino and M. Azekoff
FEMININE PERSONALITY: NEWER CONCEPTS — June 326
Natalie Shainess
FIFTEEN MINUTE HOUR — October 559
Arnold J. Mandell
FLUPHENAZINE—USE WITH CHRONIC PSYCHOTIC PATIENTS — April 211
Joseph A. Barsa and John C. Saunders
FLUPHENAZINE IN THE HOSPITALIZED PSYCHIATRIC PATIENT — June 339
Albert A. Kurland, Thomas E. Hanlon and Kay Y. Ota
FLUPHENAZINE IN TREATMENT OF PSYCHOTIC PATIENTS — September 513
John P. Holt and Eleanore R. Wright
FREE DISCUSSION IN TEACHING GROUP THERAPY TO RESIDENTS — September 527
John D. Latendresse and David F. Kennedy
FRENQUEL CORRECTS EEG CHANGES AND RELIEVES SYMPTOMS IN PORPHYRIA — December 695
Z. S. Sikes
FUNCTIONAL STRUCTURE OF THE PSYCHE — May 261
Z. O. Young
GENERAL PARESIS AND HUNTINGTON'S CHOREA—COMBINATION OF — September 507
Jane E. Oltman and Samuel Friedman
GERIATRIC HOSPITAL: ADMINISTRATION AND OPERATION — October 581
John F. Gray
GLUCAGON IN INSULIN COMA THERAPY — Supp. April 112
H. Peter Laqueur and Harry A. La Burt
GROUP THERAPY WITH LSD-25 — August 459
Bertrand Tenenbaum
HEIDEGGER'S ONTOLOGY AND HUMAN EXISTENCE — Supp. April 50
Michael Wyschogrod
HERCULEAN LABORS OF THE PSYCHIC MASOCHIST — April 218
Edmund Bergler
HOMEOSTASIS IN THE CENTRAL NERVOUS SYSTEM — December 671
George Paulson
HOSPITALS HELP MAKE ACUTE SCHIZOPHRENIA CHRONIC? — September 489
Nathaniel S. Lehrman
HUNTINGTON'S CHOREA—COMMENTS — June 313
Jane E. Oltman and Samuel Friedman

HYDROXYPHENAMATE (LISTICA) SYMPOSIUM

CHEMISTRY OF HYDROXYPHENAMATE — Supp. September 7
Charles D. Bossinger
PHARMACOLOGY AND TOXICOLOGY OF HYDROXYPHENAMATE — Supp. September 9
J. W. Bastian and G. R. Clements
HYDROXYPHENAMATE ON THE CONDITIONAL PSYCHOGALVANIC REFLEX — Supp. September 17
Leo Alexander
AMELIORATION OF ALLERGIC SYMPTOMS WITH HYDROXYPHENAMATE — Supp. September 25
Ben C. Eisenberg
EFFECT OF HYDROXYPHENAMATE ON ANXIETY STATES — Supp. September 30
Burton Cahn
USE OF HYDROXYPHENAMATE IN CARDIOVASCULAR DISEASE — Supp. September 33
Edward B. Greenspan
PHARMACOLOGICAL APPROACH TO THE TREATMENT OF HEADACHE — Supp. September 36
Arnold P. Friedman
DOUBLE BLIND STUDY INVOLVING LISTICA, LIBRIUM AND PLACEBO — Supp. September 41
Blaine E. McLaughlin, James Harris and Frank Ryan
CLINICAL TRIAL OF HYDROXYPHENAMATE IN ALCOHOLIC PATIENTS — Supp. September 44
C. Gouldman, F. Lunde and J. Davis
HYDROXYPHENAMATE IN DERMATOLOGIC THERAPY — Supp. September 47
Milton M. Cahn and Edwin J. Levy

HYDROXYZINE IN HIGH DOSAGE IN INSTITUTIONALIZED PATIENTS — September 500
Anthony Lapolla and Jesus Iberra
HYPERADRENOCORTICISM TREATED WITH CHLORPROMAZINE — December 680
Noble A. Endicott and Alexander Gralnick
HYPNOTIC AGE REGRESSION — Supp. April 118
Milton V. Kline
HYPNOSIS (CLINICAL) — Supp. April 116
Conrad M. Ayres
HYPNOSIS IN PSYCHIATRY — September 510
Herbert Spiegel
IATROCHEMISTRY, IATROPHYSICS AND IATROPSYCHOLOGY — August 463
Jerome M. Schneck
IMIPRAMINE IN OFFICE MANAGEMENT OF DEPRESSIVE REACTIONS — April 213
E. Adams Daneman
INSULIN COMA THERAPY—STUDY OF TWO METHODS — June 344
Oscar Rozett and Paul Singer
INSULIN IN PSYCHIATRIC TREATMENT — December 687
Edwin Dunlop

JEALOUSY AS A MOTIVE IN HOMICIDE ---- August 438
Edward Podolsky
JOB PLACEMENT OF EX-MENTAL PATIENTS ---- Supp. April 122
Janet I. Pinner
JUVENILE DELINQUENTS IN RESIDENTIAL TREATMENT ---- November 632
Selwyn Brody
LIBRIUM AND TARACTAN ON RETARDED CHILDREN—COMPARATIVE EFFECTS ---- October 573
T. L. Pilkington
MANAGEMENT OF LOW BACK AND SCIATIC PROBLEMS ---- September 520
F. Keith Bradford
MAO INHIBITOR THERAPY IN ADOLESCENT PSYCHIATRY ---- February 96
Robert A. Soblen and John C. Saunders
MAO INHIBITOR REACTION ---- November 641
J. Tupin
MARPLAN IN THE TREATMENT OF DEPRESSION ---- June 320
John E. Mock, Celestino Panero and Nathaniel Robinson
MEANING OF SUPERVISION TO THE PSYCHIATRIC RESIDENT ---- March 134
Norman S. Brandes
METHOHEXITAL (BREVITAL): A NEW ANESTHETIC IN ECT ---- July 388
Frank J. Ayd, Jr.
MOTIVATION FOR WORK IN PSYCHIATRIC REHABILITATION ---- Supp. April 129
George W. Brooks
"NARCISSISM" IN PSYCHOANALYSIS AND THE "LOVE OF ONESELF" IN EXISTENTIAL PSYCHOTHERAPY ---- Supp. April 69
Clemens E. Benda
NIALAMIDE IN THE TREATMENT OF DEPRESSIVE SYNDROMES ---- March 167
Adam J. Krakowski
NONCONVULSIVE ELECTROSTIMULATION ON ECT SIDE EFFECTS ---- July 382
Sidney E. Pulver and E. Gardner Jacobs
NOR-ETH-ANDROLONE (NILEVAR) ON INCONTINENCE OF MENTAL PATIENTS ---- April 225
George Vlavianos and Ludwig Fink
NORM AND PATHOLOGY OF I-WORLD RELATIONS ---- Supp. April 57
Erwin Straus
OBJECTIVE METHOD OF DETERMINING PSYCHIATRIC TREATMENT ---- February 104
Edwin Dunlop
OCCUPATIONAL THERAPY—DYNAMIC ---- Supp. April 138
H. Azima
ORGANIC THERAPY IN PEDIATRIC PSYCHIATRY ---- Supp. April 110
Lauretta Bender and Gloria Faretra
ORGANIZATION OF EX-PATIENTS OF A PSYCHIATRIC HOSPITAL ---- November 645
Jacob H. Friedman
ORTHOSTATIC HYPOTENSION SECONDARY TO PSYCHOTROPIC DRUGS ---- April 189
Kurt Witton
PARALYSIS AND SCHIZOPHRENIA CONCURRENTLY ---- April 187
Leo E. Hollister and Frederick S. Glazener
PARALYSIS AGITANS SYNDROME ---- Supp. April 86
Alfred E. Eyres
PATHOGENETIC INTERRELATIONS IN HYPERTENSION AND CORONARY DISEASE ---- Supp. April 39
Caroline Bedell Thomas
PATTERNS ---- January 13
Julius Heuscher
PERCEPTION AND PSYCHO-PHARMACODYNAMICS IN SCHIZOPHRENIA ---- May 273
G. M. Davidson and Estelle Ades
PEREGRINATING PROBLEM PATIENT ---- March 139
Warden M. Rimel and Chester M. Pierce
PERFECTIONISM AND PSEUDO-PERFECTIONISM ---- January 35
Jerome M. Schneck
PERIPHERAL PERSONALITY FUNCTION IN THE USE OF PSYCHIATRIC DRUGS ---- May 249
Edwin O. Niver
PERPHENAZINE—AN UNUSUAL COMPLICATION ---- July 398
Jacob H. Friedman, Isidore Frimmer and Subhash Vasudeva
PHARMACOTHERAPY AND ELECTROTHERAPY FOR SEVERE DEPRESSION ---- March 157
William Furst
PHENYLPYRUVIC OLIGOPHRENIA ---- August 465
Fernando Tapia
PLEASURE, PAIN AND HUMAN RELATIONS ---- April 201
Nathaniel S. Lehrman
"POOR" TREATMENT CASES—EFFECT OF DRUGS ---- December 692
Antioco R. Barron, Lester H. Rudy and Jackson A. Smith
PORPHYRIA, ACUTE INTERMITTENT: SEARCH FOR ENZYMATIC DEFECT ---- Supp. April 21
Lewis P. Rowland
PRIVATE PSYCHIATRIC PRACTICE SINCE THE END OF WORLD WAR II ---- October 547
James L. McCartney
PROKETAZINE—ANTI-PSYCHOTIC SPECTRUM ---- October 585
Anthony Sainz
PROTEIN CONTENT IN CISTERNAL FLUID OF STATE HOSPITAL PATIENTS ---- September 497
Magnus C. Petersen
PSYCHIATRIC CONSULTATION FOR RURAL PHYSICIANS ---- January 38
John S. Visher

PSYCHIATRIC TEACHING AND TRAINING PROGRAM ADVANCES ---- February 87
William L. Holt, Jr.
PSYCHIATRIC REHABILITATION RESEARCH ---- Supp. April 133
David Landy
PSYCHIATRIC RESEARCH—NEW PERSPECTIVES ---- Supp. April 46
Shervert H. Frazier
PSYCHIATRIC SERVICES TO COURTS ADVANCES ---- March 165
Richmond C. Hubbard
PSYCHIATRIC TEAM GEARED TO INTENSIVE TREATMENT ---- July 391
Lorant Forizs
PSYCHIATRY IN ISRAEL ---- August 467
Louis Miller
PSYCHIATRY IN RELATION TO MEDICAL PRACTICE ---- March 161
Anthony R. Gabriel
PSYCHIATRY IN THE NEAR EAST AND FAR EAST ---- October 583
William Holt
PSYCHOANALYTIC RESEARCH: DEVELOPMENTS ---- November 609
Robert B. White ---- December 671
PSYCHOANASYNTHESIS IN ACTION IN A MENTAL HOSPITAL ---- March 127
George Vlavianos and Ludwig Fink
PSYCHOPHARMACOLOGY IN REHABILITATION OF THE CHRONIC PSYCHOTIC ---- Supp. April 143
Sidney Merlis
PSYCHOTHERAPY: DEFINITION ---- February 106
Charles B. David
PSYCHOTHERAPY OF PSYCHOTIC PATIENTS—OBSTACLES ---- July 401
Irving M. Rosen and Ira Friedman
PSYCHOTROPIC AGENTS—COMBINED USE ---- Supp. April 81
John Gibbon
REFUSAL OF SURGICAL THERAPY ---- January 54
Jacob H. Friedman and Fannie I. Kapp
REGRESSIVE CONVULSIVE THERAPY AND LOBOTOMY IN MENTAL DISORDERS ---- April 193
James L. Sagebiel
REHABILITATION OF POST-PSYCHOTIC PATIENTS BY INDUSTRIAL WORKSHOP ---- Supp. April 125
Bertram J. Black
RETINAL DYSTROPHY TISSUE CULTURE STUDIES ---- Supp. April 14
Richard L. Sidman
SCHIZOPHRENICS' RESPONSE TO A BRAINWASHING TECHNIQUE ---- July 376
Beverley T. Mead and John P. Rollins
SCHOOL PHOBIA—DIFFICULTIES IN TREATMENT ---- February 75
Theodor Bonstedt, Donald F. Worpell and Karin Lauriat
SERUM PROTEIN FRACTIONS FROM MONGOLOIDS—STUDIES ---- February 84
Michael J. Carver and Lewis D. Welton
SEX, ANGER AND ANXIETY: INTRAPERSONAL INTERACTION IN MARRIED COUPLES ---- May 256
G. Winokur and W. R. Gaston
SIDE-EFFECTS AND TOXICITY OF PSYCHOPHARMACOLOGIC AGENTS ---- Supp. April 97
Reuben M. Cares and Charles Buckman
SOCIAL CLASS AND USE OF HYPNOTICS IN DEPRESSIVES ---- July 396
James B. Allison and J. Cornell DeWitt
SPECTROGRAPHIC AND CHROMATOGRAPHIC STUDIES IN PSYCHOTICS ---- November 619
Thomas M. Runge, Sidney W. Bohls, Sam A. Hoerster, Jr., and Nawasa Thurman
STATUS AND USEFULNESS OF THE PSYCHIATRIST ---- December 697
Thomas R. Kearney
SUICIDE IN A MENTAL HOSPITAL ---- July 365
Arnold R. Beisser and James E. Blanchette
SUPERIORITY, SERVICE AND STANDARDS ---- August 423
Mathew Ross
TARACTAN: CLINICAL EXPERIENCE ---- January 40
F. Cornu and H. Hoffet
TARACTAN (CHLORPROTHIXENE) AS A NEUROLEPTIC DRUG ---- September 502
Heinrich Gross and Elfriede Kaltenbaeck
TESTOSTERONE AS ADJUVANT IN TREATMENT OF SCHIZOPHRENICS ---- August 443
Leonard I. Lapinsohn
THALIDOMIDE: SURVIVAL FOLLOWING OVERDOSE ---- January 52
Guenther Neuhaus and Karla Ibe
THERAPEUTIC COMMUNITY AND ITS BENEFITS ---- May 265
Alexander Gralnick
THIORIDAZINE HYDROCHLORIDE: CLINICAL STUDY ---- March 149
Nina Kateryniuk
THIORIDAZINE (MELLARIL) IN PSYCHOLOGICAL DISORDERS ---- June 330
R. Bruce Sloane and Philip Haden
THYROID (THE): GENETIC AND PSYCHIATRIC RELATIONS ---- Supp. April 33
Sidney C. Werner
TRANQUILIZERS IN CHRONIC ILLNESS ---- August 457
John L. Otto
TRANQUILIZERS AND CHILD ANALYSIS IN CHILD PSYCHIATRY ---- August 434
Herbert Freed
TRANQUILIZER EVALUATION IN GENERAL PRACTICE ---- March 151
A. Lewis Kolodny

TRANQUILIZING DRUGS—SUBJECTIVE FEELINGS ABOUT THEM ---- July 408
Lewis J. Sherman
TRIFLUOPERAZINE IN ANXIETY ASSOCIATED WITH ORGANIC DISORDERS ---- September 525
Fred J. Phillips and David M. Shoemaker
TRIFLUOPERAZINE—A CLINICAL TRIAL STUDY ---- November 639
Nina Kateryniuk and Charles W. Morris
TRILAFON THERAPY: COMPLICATIONS ---- January 32
Henry R. Olivier and Max Sugar
UK-738 IN THE THIOPERAZINE-INDUCED EXTRAPYRAMIDAL REACTION ---- October 571
William Mandel, Bessie Claffey and Lester H. Margolis
VALMETHAMIDE IN PSYCHIATRIC OUT-PATIENT CARE ---- June 346
Martin Goldberg

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